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CASE REPORT | SMALL BOWEL

Nonhepatic Hyperammonemic Encephalopathy: An Unmasked Urea Cycle Disorder in the Setting of Late Gastric Bypass Complication

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ABSTRACT

We present the case of a woman with nonhepatic hyperammonemic encephalopathy, a rare complication of bariatric surgery. Proposed mechanism include underlying urea cycle disorders and increased ammonia production. Clinically, states of hyperammonemia present with predominantly neurological symptoms of behavioral disturbances, lethargy, seizures, and coma. Given the high morbidity and mortality rate of nearly 40%, early recognition and treatment of the underlying mechanisms of hyperammonemia are crucial.

KEYWORDS: gastric bypass; roux-en-Y gastric bypass; RYGB; urea cycle disorder; obesity; malnutrition

INTRODUCTION

Nonhepatic hyperammonemic encephalopathy (NHAE) is a rare complication of bariatric surgery with an associated morbidity and mortality rate of nearly 40%. Its pathogenesis remains largely unclear; however, proposed mechanisms include underlying urea cycle disorders in the setting of an increased protein load seen in catabolic states, increased ammonia production such as in bacterial overgrowth, and decreased ammonia clearance. Clinically, states of hyperammonemia present with predominantly neurological symptoms of behavioral disturbances, lethargy, seizures, and coma and may be precipitated by any number of stressors resulting in a catabolic state, such as acute illness. Given the high morbidity and mortality, early recognition, and treatment of the underlying mechanisms of hyperammonemia are crucial. We present a case of nonhepatic hyperammonemic encephalopathy, with a particular focus on clinical presentation, the diagnostic schema of an underlying inborn error of urea cycle metabolism, and the approach to treatment.

CASE REPORT

A 49-year-old woman with class III obesity, fatty liver disease without evidence of cirrhosis, prior alcohol use disorder, opiate use disorder maintained on methadone, severe venous insufficiency, and a history of Roux-en-Y gastric bypass (RYGB) surgery 7 years prior with poor postoperative follow-up experienced recurrent encephalopathy warranting several hospital admissions. She was again admitted on this occasion for several hours of altered mental status, increased weakness, and aggressive behavior.

She presented vitally stable with a body mass index of 56 kg/m^2. Her physical examination revealed an obtunded female with asterixis and diffusely decreased muscle tone, a large obese abdomen with woody cobblestoning, significant lower extremity edema with cobblestoning pattern up to the level of her groin, and superficial desquamation of bilateral feet. The initial laboratory workup was remarkable for severe hypoalbuminemia to the level of 1.9, elevated international normalized ratio to 4.5, hyperammonemia to 104, mild elevation in aspartate aminotransferase, and modest direct and indirect hyperbilirubinemia. Given her mental state and laboratory findings, we opted for computed tomography of the head, resulting without acute findings, as well as an abdominal ultrasound and contrast-enhanced computed tomography, resulting without evidence of cirrhosis, portal hypertension, or portal

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vein thrombosis, but revealing diffuse anasarca. We initially suspected toxic metabolic encephalopathy in relation with chronic recurrent cellulitis of her lower extremities due to long-standing venous stasis dermatitis; however, infectious workup remained negative, and despite antibiotic treatment, her mental state continued to waver. We opted to attempt to treat for questionable hepatic encephalopathy despite the lack of evidence of cirrhosis given her remote history of alcohol use disorder. Aggressive use of lactulose, daily rifaximin, and near daily trends of ammonia proved to be ineffective with frequent bounce back admissions to the hospital with similar presentations. During her latest and longest hospital stay amounting to >100 days, she unfortunately suffered a sequela of complications including mild coronavirus disease 2019 infection, anuric acute tubular necrosis diagnosed by renal biopsy requiring temporary dialysis, recurrent postprandial hypoglycemia deemed to be related to late dumping syndrome, *Klebsiella* urinary tract infection with bacteremia, and pressure-related injuries to lower extremities with underlying chronic venous stasis.

Throughout these complications, her mental state wavered periodically. We opted to look for other reasons for her hyperammonemic state which prompted a nutritional workup. This workup revealed several nutritional deficiencies, including low levels of zinc, copper, and many amino acids including citrulline, arginine, asparagine, a high level of ornithine, and normal urine orotic acid levels. Although closely related to the underlying liver disease, findings of elevated international normalized ratio, thrombocytopenia, and elevated bilirubin were attributed to her malnutritional state, and largely improved by the end of her hospital stay (Table 1).

With consultation with a Geneticist, Hepatologist, and Bariatric Surgeon, we came to the possibility of nonhepatic hyperammonemia related to her prior gastric bypass and occult previously nonclinically apparent urea-cycle disorder as a consideration, namely carbamoyl phosphate synthetase 1 (CPS 1) deficiency given deficiency in citrulline. Although the mechanism is largely unknown, we reviewed case reports with similar presentations where a history of RYGB unmasked patients' underlying urea cycle disorders through various mechanisms such as nutritional deficiencies and increased states of catabolism.

Once we established this probable diagnosis in our patient, we first endeavored to halt ammonia production by reversing the catabolic process in her severe malnutritional state with IV dextrose and trending serum ammonia levels until they had normalized. Once her acute medical issues were stabilized, we changed our focus to improve her baseline nutrition, late complications of her remote RYGB. We temporized with low-protein total parenteral nutrition (TPN) while the possibility of bypass reversal was entertained. The indications for this were 2-fold—to help improve her nutritional status and to reverse the ammonia-producing bacterial overgrowth within the blind loop.

Table 1. Laboratory values

Laboratory value	Patient value	Normal range
Albumin	1.9 g/dL	3.2–5.1 g/dL
International normalized ratio	4.5	<1.1
Ammonia	104 g/dL	15–45 μg/dL
White blood cell count	570/μL 4,000-11,000/μL	
Plate	150,000/μL	150–450 L
Glucose	69 mg/dL	70–99 mg/dL
Urea	17 mg/dL	7–20 mg/dL
Creatinine	1.01 mg/dL	0.6-1.2 mg/dL
Sodium	144 mmol/L	135–145 mmol/L
Potassium	4.3 mmol/L	3.5–5.0 mmol/L
Magnesium	1.9 mmol	1.7–2.2 mmol/L
Calcium	7.7 mmol/L	8.5–10.2 mg/dL
Phosphorus	5.4 mmol/L	2.5–4.5 mg/dL
Aspartate aminotransferase	68 IU/L	0-35 IU/L
Alanine aminotransferase	28 IU/L	0-35 IU/L
Alkaline phosphatase	85 IU/L	44-147 IU/L
Total bilirubin	3.5 mg/dL	0.3–1.0 mg/dL
Direct bilirubin	2.6 mg/dL	0.0–0.3 mg/dL
pH	7.46	7.35–7.45
Bicarbonate	22 mg/dL	21–28 mmol/L
PCO2	40 mm Hg	35–45 mm Hg
Lactate	2.4 mmol/L	0.5–2.2 mmol/L
Zinc	38 mcg/dL	60–120 mcg/dL
Copper	36 mcg/dL	70–140 mcg/dL
Citrulline	13 μmol/L	16–35 μmol/L
Arginine	42 μmol/L	35–100 μmol/L
Asparagine	18 μmol/L	16–40 μmol/L
Ornithine	117 μmol/L	70–120 μmol/L
Urine orotic acid	Normal	—

We were ultimately able to wean her from TPN to a simple amino acid tube feed with trace elements with sufficient calories to maintain the anabolic state and correct her severe malnutrition. From there, she gradually transitioned to a primarily oral diet, with stable ammonia levels.

We continued supportive management with lactulose, rifaximin, and dense caloric support through TPN along with repletion of amino acids, vitamins, and minerals to prevent ammonia production and accumulation and reverse protein catabolism. Although not available in our institution, ammonia scavenging agents may also help prevent metabolic decompensation.

We involved bariatric surgery to establish whether bypass reversal of the remote surgery would prove to be beneficial; however, this was not pursued, given concern of several

complications relating to her already complicated and prolonged hospital course. Instead, we inserted robotic-assisted Stamm gastrostomy tube with gastric and jejunal ports into the remnant stomach for the initiation of tube feeds. This successfully weaned her off TPN with gradual transition to oral diet with an emphasis on low protein to reduce ammonia production and to encourage an anabolic state. The patient's clinical condition gradually improved with stable ammonia levels.

DISCUSSION

Hyperammonemia is defined as excess levels of ammonia, a nitrogen-containing compound produced in the intestines and transported to the liver for breakdown through the urea cycle to water-soluble urea for urinary excretion. In excess, the urea cycle cannot break down ammonia effectively, leading to the crossing of the blood-brain barrier and subsequent encephalopathy. Hyperammonemia is an established cause of encephalopathy, usually related to cirrhosis due to defective liver function, reducing its ability to metabolize ammonia through the urea cycle.[1,2]

Causes of hyperammonemia are primary or secondary.[5] Primary causes include congenital disorders of the urea cycle enzymes, most commonly a deficiency in ornithine transcarbamylase. Expression can be variable depending on the extent of the enzyme defect. Secondary causes can be hepatic or nonhepatic, where liver dysfunction promoting portosystemic shunting with systemic release of excess ammonia is the most common. Nonhepatic causes include some hematological disorders, urease-producing bacterial infections, unmasked urea cycle disorders with heterozygosity for deficiency of enzymes, and some medications.[5,6]

Nonhepatic hyperammonemic encephalopathy is a rare and relentless complication of RYGB surgery. It can be a late complication of the surgery, sometimes up to 20 years after, and one proposed mechanism is thought to be related to underlying urea cycle disorders. It has a high morbidity of up to 40% and takes significant metabolic control to prevent recurrent encephalopathy.

RYGB surgery is one of the most common weight loss surgeries in the United States. It involves creating the following: a gastric pouch at the proximal stomach, biliopancreatic limb, jejunojejunostomy, and gastrojejunostomy,[3] thereby bypassing most of the stomach, duodenum, and proximal jejunum. The surgery attains weight loss by restrictive and malabsorptive mechanisms leading to a catabolic state, with a subsequent increase in ammonia byproduct. Normally, the liver can break the ammonia down to urea. However, in cases where an underlying urea cycle enzyme deficiency exists in times of high physiological stress, ammonia cannot be broken down as readily.

Given the rarity of the condition, there has been one review to date collecting data from 33 patients that fit the criteria of developing nonhepatic hyperammonemic encephalopathy post-RYGB.[4] Other proposed mechanisms are attributed to increased ammonia production from a proteolytic catabolic state, impaired citrulline synthesis resulting in a disordered urea cycle, L-carnitine deficiency, malnutrition leading to decreased production of urea cycle enzymes, coagulated blood in the remnant stomach leading to slow breakdown and accumulation of ammonia, urealytic bacterial strains in gastric pouch, vascular shunts, and excessive protein intake.[4]

Symptoms of NHAE are typical of hyperammonemia, including altered mentation, confusion, asterixis, agitation, irritability, nausea, vomiting, seizures, coma, and death. Alternative diagnoses should be considered and treated, if applicable. These diagnoses include Wernicke encephalopathy resulting from thiamine deficiency due to severe malnutrition, vitamin B12 deficiency, copper deficiency, decompensated cirrhosis, intracranial pathologies, and D-lactate acidosis. Diagnosis of NHAE requires a high clinical suspicion, particularly given its rare prevalence. It remains a diagnostic challenge with delays in diagnosis lending to its high morbidity. Workup should include assessing levels of serum and urine amino acids, urine orotic acids, and cofactors of the urea cycle zinc, copper, and L-carnitine.

Once cardiovascular and respiratory systems are stabilized, patients typically require monitoring in an intensive care unit. Treatment thereafter surrounds decreasing ammonia levels, including the use of lactulose, rifaximin, and strict nutritional support. Nutritional support should begin with micronutrient repletion and high glucose infusion, such as infusion with 5% dextrose, to reverse the catabolic state. Once ammonia is decreased and there is clinical improvement, dense caloric support through total parenteral nutrition is used. In our patient, given her complex comorbidities and severe illness, surgical reversal of her RYGB anatomy was not possible, so instead, we opted for stimulation of her remnant stomach with the use of tube feeds to decrease urease-producing bacteria burden and to reverse her state of malnutrition.

Another consideration in cases with hyperammonemia due to urea cycle disorders is the use of ammonia scavenging agents. Given their cost and limited availability in our institution, our patients did not receive these compounds, however, could benefit.

Hyperammonemia, regardless of the cause, is a severe and potentially fatal disease. NHAE remains to be a diagnostic challenge with unclear mechanisms responsible. Further research and awareness of the disease is imperative for timely recognition and treatment.

DISCLOSURES

Author contributions: T. Samardzic: corresponding author, writing original draft, review, editing and is the article guarantor. R. Zeghlache: writing/draft editing, review, data curation. K. Norman: conceptualization, supervision, draft editing.

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