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CASE REPORT | LIVER

Hyperammonemia Encephalopathy due to Urea Cycle Disorder Precipitated by Gastrointestinal Bleed in the Setting of Prior Bariatric Surgery

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ABSTRACT

The urea cycle is a metabolic pathway that excretes nitrogenous waste products from the body. Urea cycle disorders (UCDs) result from enzymatic deficiencies within this pathway, which can lead to life-threatening hyperammonemia. Gastric bypass-related hyperammonemia in patients who have undergone Roux-en-Y gastric bypass surgery has been previously reported. UCDs have been implicated as a cause of gastric bypass-related hyperammonemia. In this report, we present the case of a patient with a history of bariatric surgery who experienced severe hyperammonemia encephalopathy triggered by a gastrointestinal bleed due to an undiagnosed UCD.

KEYWORDS: hyperammonemia encephalopathy; urea cycle disorder; ornithine transcarbamylase deficiency; gastric bypass-related hyperammonemia; bariatric surgery; gastrointestinal bleed

INTRODUCTION

The urea cycle is a metabolic pathway that converts nitrogen to urea for excretion from the body. Urea cycle disorders (UCDs) result from a deficiency of enzymes within this pathway, which can lead to hyperammonemia and life-threatening metabolic and neurologic complications. The estimated prevalence of UCDs is 1 in 35,000 live births in the United States.[1] In a longitudinal study of 614 patients with UCDs, the mortality rate was found to be 24% in neonatal-onset cases and 11% in late-onset cases.[1] Among the UCDs, ornithine transcarbamylase (OTC) deficiency, an X-linked semidominant disorder, is the most common, with an estimated incidence of 1 in 56,500 live births.[2] Neonates can present with lethargy, malnutrition, seizures, coma, and death if left untreated. Adult patients can be asymptomatic throughout life or develop hyperammonemia-related symptoms after a physiological stress trigger. Adults can have an atypical presentation that includes headaches, altered mental status, behavioral abnormalities, and cyclic vomiting.[3]

In this report, we present the case of a patient with a history of bariatric surgery who experienced severe hyperammonemia encephalopathy triggered by a gastrointestinal (GI) bleed due to an undiagnosed UCD.

CASE REPORT

A 41-year-old woman with a history of Roux-en-Y gastric bypass (RYGB) 16 years earlier, iron deficiency anemia, and bipolar disorder presented to our facility with fatigue and melena. She underwent extensive endoscopic and radiological workup, including a nuclear bleeding scan, with findings suspicious for active GI bleeding within the excluded limb of the duodenum. She underwent laparoscopic-assisted endoscopy in conjunction with bariatric surgery, revealing a bleeding ulcer in the duodenal bulb, classified as Forest Class 1B. Successful endoscopic hemostasis was achieved through epinephrine injection, thermal therapy, and one endoclip. Two days later, she developed recurrent GI bleeding with hemorrhagic shock requiring exploratory laparotomy, duodenotomy, and bleeding ulcer vessel ligation. GI bleeding was controlled, and the patient was discharged home with advice to avoid nonsteroidal anti-inflammatory drugs and to continue taking a proton-pump inhibitor.

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After 2 weeks, the patient presented to the hospital for altered mental status in the form of periodic episodes of confusion and somnolence. Initial laboratory workup revealed a glucose level of 45 mg/dL (reference range, 70–99 mg/dL) and a new cholestatic pattern of liver injury with an alkaline phosphatase of 216 U/L (reference range, 30–115 U/L), total bilirubin of 4.3 mg/dL (reference range, 0.2–1.2 mg/dL), and direct bilirubin of 3.2 mg/dL (reference range, 0.0–0.3 mg/dL). Aminotransaminase levels, international normalized ratio, and platelet counts were normal.

Intravenous glucose and thiamine supplementation was initiated; however, her mental status continued to worsen, and the patient was nonresponsive to painful stimuli. Infectious etiology was ruled out, and radiological workup, including noncontrast computed tomography (CT) and magnetic resonance imaging of the head, was unremarkable. Ultrasound, CT, and magnetic resonance imaging of the abdomen were unremarkable, except for hepatic steatosis. An electroencephalogram demonstrated epileptiform discharges and slowing indicative of severe encephalopathy, and she was started on levetiracetam. The ammonia level was found to be elevated at 200 μmol/L (reference range, 11.0–55.0 μmol/L) while the zinc level was low (38 μg/dL) (reference range, 44–115 μg/dL).

The patient was started on lactulose 30 mL every 6 hours, rifaximin 550 mg twice daily, and zinc sulfate replacement of 50 mg daily. Within 48 hours of initiating treatment, her ammonia level decreased to 151 μmol/L, and within 4 days, it normalized completely, leading to an improvement in her mental status. The cholestatic pattern of liver injury gradually normalized and was believed to be drug-induced by antibiotics (piperacillin-tazobactam) she had received on her prior admission. Her hyperammonemia encephalopathy was suspected to be a long-term complication of her prior gastric bypass surgery and precipitated by her recent GI bleed, and given that no cirrhosis or portal shunt was seen on CT, a UCD needed to be ruled out. Her plasma amino acid analysis revealed an elevated glutamine level of 808.7 μmol/L (reference range, 372.8–701.4 μmol/L), a low citrulline level of 7.3 (reference range, 15.6–46.9 μmol/L), and a normal arginosuccinate level of $<$0.1 μmol/L (reference range, 0.0–3.0). Serum analysis suggested a biochemical diagnosis of heterozygosity for OTC deficiency, an X-linked UCD. By hospital day 16, the patient's mental status was completely back to normal, and she was discharged home on lactulose, rifaximin, and zinc supplementation.

DISCUSSION

We report the case of an adult woman who developed hyperammonemia encephalopathy 2 weeks after being hospitalized for a complicated GI bleed. Her history of RYGB surgery predisposed her to develop hyperammonemia in the setting of heterozygous OTC deficiency, likely triggered by the physiologic stress of the GI bleed. She was lost to follow-up, and urine orotic acid and genetic testing were not conducted. However, given that the patient was female with an elevated glutamine, normal arginosuccinate, and low citrulline, these findings are suggestive of heterozygous OTC deficiency. Patients with heterozygous OTC deficiency can sometimes have normal genetic testing and still have low OTC enzyme function.

The incidence of duodenal ulcers is less common after gastric bypass surgery as compared with marginal ulcers.[4] Marginal ulcers occur at or near the intestinal side of a gastrojejunal anastomosis and are a common complication of RYGB surgery, seen in up to 16% of patients.[5] Most marginal ulcers are seen within 1 year after RYGB.[5] Our patient presented with GI bleed from an ulcer in the excluded part of the duodenum 16 years after the bypass surgery.

It has previously been reported that there are less than 25 known cases worldwide of hyperammonemia encephalopathy associated with RYGB in the absence of cirrhosis.[6] Bariatric surgery is considered a cause of nonhepatic hyperammonemia.[6,7] The mechanism by which hyperammonemia occurs because of RYGB is not fully understood, but is believed to be multifactorial. Factors that play a role include increased states of catabolic stress, disruption of intestinal flora leading to increased nitrogenous waste products, and nutritional deficiencies, among others.[6–8]

UCDs typically manifest in the newborn period with signs of lethargy, vomiting, and even coma after initial feeding provides a protein load that the infant is unable to metabolize, leading to hyperammonemia. All UCDs are inherited in an autosomal recessive pattern, except for OTC deficiency, which is X-linked. Therefore, heterozygous female carriers have a range of clinical severity from asymptomatic to life-threatening coma depending on the pattern of lyonization. Most female carriers will remain asymptomatic during their lifetime; however, certain conditions can trigger symptomatic late-onset OTC deficiency. There are case reports highlighting previously asymptomatic OTC-deficient heterozygous female carriers who developed life-threatening hyperammonemia in the postpartum period.[9] Fenves et al[10] conducted a retrospective review of 20 patients with a history of RYGB who developed hyperammonemia encephalopathy and described the syndrome as gastric bypass-related hyperammonemia (GaBHA). The onset of the hyperammonemia encephalopathy ranged from 1 month to 28 years after surgery with a reported mortality rate of 50%.[10] Of 20 cases, 19 were female, highlighting the role of an X-linked risk factor associated with this syndrome and thus implicating OTC deficiency as a major potential factor.[10]

The diagnosis of hyperammonemia encephalopathy can be made by confirming an elevated blood ammonia level in patients with altered mental status. Treatment of GaBHA is aimed at lowering ammonia levels, primarily using lactulose and rifaximin.[6] Patients who respond to treatment with lactulose and rifaximin support the diagnosis of hyperammonemia encephalopathy. Our patient quickly responded to lactulose and rifaximin with rapid improvement in her ammonia level, and therefore, treatments such as dialysis and other pharmacological nitrogen-scavenging agents were not used. Other methods include repleting deficient amino acids, micronutrients, glucose supplementation, and zinc. Zinc deficiency has been believed to play a role in OTC deficiency

because zinc supplementation has increased OTC activity in cirrhotic rats.[11] Zinc is largely regulated by the liver, acts as a cofactor for many enzymes, and plays an important role in cell growth and development.[12] In the review by Fenves et al[10] of 20 cases of GaBHA, zinc levels were low in 9 of 11 tested patients. In our patient, it is possible that zinc supplementation had an indirect role in increasing her OTC activity, thereby improving her urea metabolism. Other invasive measures for GaBHA that have been reported include surgical reversal of the RYGB[13] and occlusion of a splenorenal shunt.[14]

In summary, we present a woman with a history of RYGB found to have heterozygous OTC deficiency who developed hyperammonemia encephalopathy after a complicated GI bleed. This case can be described as part of the syndrome of GaBHA. GaBHA and OTC deficiency are under-recognized, and clinicians should be aware of these syndromes in any patient who develops hyperammonemia encephalopathy.

DISCLOSURES

Author contributions: J. Loeffler: writing the manuscript, data gathering, and literature review and is the article guarantor. A. Elfiky: conceptual design, data analysis, and manuscript review. H. Al Moussawi and N. Ravindran: review and revision of the manuscript.

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REFERENCES

1. Batshaw ML, Tuchman M, Summar M, Seminara J; Members of the Urea Cycle Disorders Consortium. A longitudinal study of urea cycle disorders. *Mol Genet Metab*. 2014;113(1–2):127–30.
2. Summar ML, Koelker S, Freedenberg D, et al. The incidence of urea cycle disorders. *Mol Genet Metab*. 2013;110(1–2):179–80.
3. Smith W, Kishnani PS, Lee B, et al. Urea cycle disorders: Clinical presentation outside the newborn period. *Crit Care Clin*. 2005;21(4 Suppl): S9–17.
4. Gumbs AA, Duffy AJ, Bell RL. Incidence and management of marginal ulceration after laparoscopic Roux-Y gastric bypass. *Surg Obes Relat Dis*. 2006;2(4):460–3.
5. Sacks BC, Mattar SG, Qureshi FG, et al. Incidence of marginal ulcers and the use of absorbable anastomotic sutures in laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2006;2(1):11–6.
6. Nagarur A, Fenves AZ. Late presentation of fatal hyperammonemic encephalopathy after Roux-en-Y gastric bypass. *Proc (Bayl Univ Med Cent)*. 2017;30(1):41–3.
7. Rosenberg C, Rhodes M. Hyperammonemia in the setting of Roux-en-Y gastric bypass presenting with osmotic demyelination syndrome. *J Community Hosp Intern Med Perspect*. 2021;11(5):708–12.
8. Koffman BM, Greenfield LJ, Ali II, Pirzada NA. Neurologic complications after surgery for obesity. *Muscle Nerve*. 2006;33(2):166–76.
9. Arn PH, Hauser ER, Thomas GH, Herman G, Hess D, Brusilow SW. Hyperammonemia in women with a mutation at the ornithine carbamoyltransferase locus. A cause of postpartum coma. *N Engl J Med*. 1990; 322(23):1652–5.
10. Fenves AZ, Shchelochkov OA, Mehta A. Hyperammonemic syndrome after Roux-en-Y gastric bypass. *Obesity (Silver Spring)*. 2015;23(4): 746–9.
11. Aquilio E, Spagnoli R, Riggio D, Seri S. Effects of zinc on hepatic ornithine transcarbamylase (OTC) activity. *J Trace Elem Electrolytes Health Dis*. 1993; 7(4):240–1.
12. Himoto T, Masaki T. Associations between zinc deficiency and metabolic abnormalities in patients with chronic liver disease. *Nutrients*. 2018; 10(1):88.
13. Estrella J, Yee G, Wilcken B, Tchan M, Talbot M. Hyperammonemic encephalopathy complicating bariatric surgery: A case study and review of the literature. *Surg Obes Relat Dis*. 2014;10(3):e35-e38.
14. Rogal SS, Hu A, Bandi R, Shaikh O. Novel therapy for non-cirrhotic hyperammonemia due to a spontaneous splenorenal shunt. *World J Gastroenterol*. 2014;20(25):8288–91.

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