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BRIEF COMMUNICATION

Recurrent Hyperammonemia During Enteral Tube Feeding for Severe Protein Malnutrition After Bariatric Surgery

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Abstract

A 28-year-old female was admitted 2 years after gastric bypass limb distalization because of severe weight loss, fatigue, chronic diarrhea, massive edema, and a serum albumin of 10 g/L without proteinuria. A diagnosis of severe energy and protein malnutrition was made, and enteral tube feeding was started in combination with pancreatic enzyme supplementation every 3 h. Within 24 h after the start of tube feeding, she developed severe hyperammonemia. Tube feeding was stopped immediately, and this led to a normalization of serum ammonia levels within 8 h. When tube feeding was resumed, albeit at a lower rate and with preventive measures taken, hyperammonemia occurred again. The underlying causes and treatments of hyperammonemia during tube feeding are discussed.

Keywords Refeeding · Hyperammonemia · Gastric bypass · Bariatric surgery · Protein malnutrition · Enteral tube feeding · Urea cycle

Introduction

Severe protein malnutrition, defined as a serum albumin < 25 g/L, is one of the most dangerous nutritional complications that may develop after bariatric surgery. It is associated with increased morbidity and mortality and requires timely diagnosis and appropriate treatment [1]. The impulse to start treatment with high-protein feeding is not without risk and may be fatal, in particular in patients presenting with a combination of severe calorie and protein depletion. Such patients are at risk to develop severe non-hepatic hyperammonemia which may result in coma and even death [2, 3].

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Case

A 28-year-old woman was admitted because of severe fatigue, weakness, chronic diarrhea, and generalized edema. Seven years previously, she had received a Roux-en-Y gastric bypass for morbid obesity. This was followed by a limb distalization 5 years later because of weight regain from 102 to 137 kg, and a BMI of 44.8 kg/m^2. After distalization (alimentary limb 300 cm, biliary limb 50 cm, common channel 100 cm), she developed loose stools up to seven times a day, and chronic weight loss that increased to 65 kg in 2 years. On physical examination, she had a body weight of 72 kg, BMI of 22.7 kg/m^2, blood pressure of 110/80 mm Hg, and generalized edema of the legs and abdominal up to the chest. Laboratory screening was as follows: Hb 5.4 mmol/L, creatinine 60 μmol/L, potassium 3.9 mmol/L, bicarbonate 30 mmol/L, albumine 10 g/L without proteinuria, fasting glucose 3.7 mmol/L with a HbA1c < 15 mmol/mol (normal range (NR), 20–42 mmol/mol), slightly elevated liver enzymes (ASAT 42 U/L, ALAT 30 U/L, alkaline phosphatase 172 and yGT 182), normal coagulation tests, and a venous ammonia level of 31 μmol/L (NR, < 50 μmol/L). Folic acid, vitamin B_{12}, ferritin, and B_1 levels were normal, whereas zinc (4.0 μmol/L; NR, 9.2–18.4),

selenium (0.09 μmol/L; NR, 0.63–1.52), vitamin A (below detection level of 0.35 μmol/L), and vitamin D (40 nmol/L) were well below the normal range despite the daily use of a multivitamin containing retinol palmitate 1100 IU and cholecalciferol 3000 IU (WLS Forte®, FitForMe, Rotterdam, The Netherlands). A provisional diagnosis of severe energy and protein malnutrition was made, and nasal-jejunal tube feeding was started according to a recently described protocol [4]. Perative® (Abbott, UK: 130 kcal/100 mL, protein content 6.7 g/100 mL) administered continuously over 24 h at a rate of 500 mL/24 h, combined with oral supplementation of a pancreatic enzyme mixture (Panzytrat®, Pharm-Allergan GmbH, Germany) every 3 h during the day and continued during the night to improve digestion and absorption. Spironolactone 50 mg once a day was started to reduce edema, and laboratory screening for refeeding syndrome was ordered three times a week. Within 24 h after the start of tube feeding, the patient felt unwell and reported nausea and vomiting. Laboratory results showed a severely elevated ammonia level of 196 μmol/L, and tube feeding was stopped immediately (Fig. 1(mark 1)) whereupon ammonia levels decreased rapidly to 62 μmol/L the same evening. The next morning, at an ammonia level of 34 μmol/L, tube feeding was resumed, but at a slower rate, i.e., 250 mL/24 h. Nevertheless, plasma ammonia measured in the late evening had increased again, now to 133 μmol/L. Tube feeding was stopped again and replaced by continuous high-dose intravenous glucose infusion at a rate of 400 g/24 h to block ammonia production induced by endogenous protein catabolism (Fig. 1(mark 2)). The next morning, when ammonia level had decreased to 33 μmol/L, tube feeding was resumed at a rate of 250 mL/24 h, under continuation of intravenous glucose infusion (Fig. 1(mark 3)). Ammonia levels now stayed within normal range, and tube feeding was gradually raised. When tube feeding was increased to 750 mL/24 h, the evening ammonia level increased to 110 μmol/L whereupon the tube feeding rate was reduced to 500 mL/24 h (Fig. 1(mark 4)). The next morning, when plasma ammonia had decreased to 63 μmol/L, tube feeding was gradually increased by 100 mL/24 h each day, combined with a check of ammonia levels in the early morning and late evening. As morning levels remained close to the normal range and the peak levels in the evening remained less than 150 μmol/L, this regimen was continued. However, when tube feeding was increased to 800 mL/24 h, a sudden rise in the evening plasma ammonia up to 251 μmol/L was observed, despite the continuation of glucose infusion at 300 g/24 h (Fig. 1(mark 5)). The patient was a little nauseous but showed no signs of confusion or drowsiness. Tube feeding was stopped immediately, and in the next morning, plasma ammonia levels were again within the normal range. An explanation for the unexpected high rise of ammonia in the evening was found at the patient's bedside table. A visitor had brought a KFC bucket of chicken nuggets containing 117 g of protein which the patient had happily accepted and consumed. After normalization of plasma ammonia and instruction by the dietician to

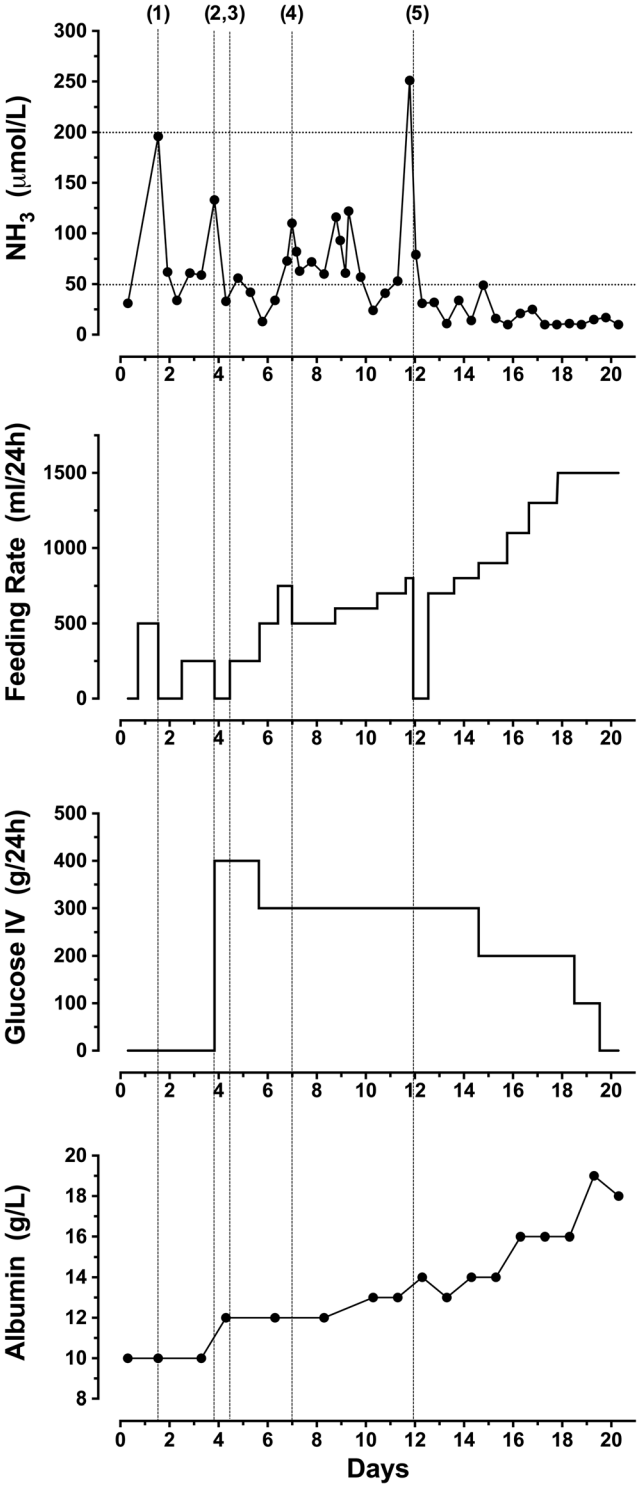

Fig. 1 Plasma ammonia levels during tube feeding in a patient with severe protein malnutrition, developed after gastric bypass limb distalization. Acute hyperammonemia with levels exceeding 200 μmol/L is associated with an increased risk of irreversible cerebral damage [5, 6]

avoid excessive protein loads, tube feeding was resumed at a rate of 700 mL/24 h and could be gradually increased up to 1500 mL/24 h, without events. Simultaneously, glucose infusion was gradually reduced and eventually stopped. Twenty days after the start of tube feeding, the patient was discharged, without edema and with a serum albumin of 18 g/L and ammonia level of 10 μmol/L. Two months later, at an albumin of 24 g/L, she decided to remove the feeding tube and was lost to follow-up.

Discussion

This case illustrates that post-bariatric patients with severe energy and protein malnutrition are at risk to develop acute hyperammonemia with levels in the neurotoxic range, even if enteral feeding is started at a low rate. Acute rises in plasma ammonia levels are highly dangerous because they may lead to rapidly developing cerebral edema, coma, and even death [2, 3, 5]. The present patient is rather exceptional because she developed severe hyperammonemia with a protein infusion rate as low as 33 g/24 h. It took some time before we realized that there was a pattern, with morning ammonia levels within or close to the normal range and marked elevations in the late evening samples. Eventually, an empty KFC bucket on the bedside table previously containing chicken nuggets offered a plausible explanation. It represented a protein load of 117 g in a patient already at risk to develop hyperammonemia. Retrospectively, the ammonia peaks observed in the preceding days were also likely to be related to intermittent protein loads. She had been allowed to take her meals as tolerated, and the hot meals provided in the evening were a likely explanation for the evening ammonia peaks. After the ammonia peak on day 11, she received extensive dietary instruction to prevent excessive protein loads, and hyperammonemia was no longer observed, despite a gradually increase in tube feeding rate.

About 90% of adult hyperammonemia is caused by severe liver disease, the remaining 10% is related to rare circumstances characterized by either increased ammonia production, reduced elimination, or a combination of both [5–7].

In catabolic post-bariatric patients, non-hepatic hyperammonemia is most likely caused by a combination of enhanced proteolysis, acquired urea cycle enzyme deficiencies, severe zinc deficiency, and excessive protein feeding. Enhanced intestinal ammonia production caused by bacterial overgrowth, or medication inhibiting urea cycle function, may also play a role [3, 5, 6]. In these patients, protein feeding should be stopped immediately, and proteolysis and gluconeogenesis should be blocked by high-dose glucose infusion. If this is insufficient, ammonia production can be reduced by infusion of sodium benzoate (Ammonul®, Valeant Pharmaceuticals International Incl., Canada), sodium phenylacetate (Buphenyl®, Horizon Pharma, Ireland), or glycerol phenylbutyrate (Ravicti®, Horizon Pharma, Ireland). These substances bind to glycine and glutamine to form hippuric acid and phenylacetylglutamine, respectively, and thus prevent ammonia production by blocking glycine and glutamine catabolism. Both hippuric acid and phenylacetylglutamine are rapidly excreted by the kidneys [5, 8]. Arginine infusion can be used to promote the production of ornithine, the key amino acid of the urea cycle, to improve NH3 conversion to urea [7]. Next, other sites of ammonia production should be dealt with. Intestinal ammonia production can be reduced by the administration of lactulose and rifaximin. Lactulose (Duphalac®, Abbott Biologicals BV, The Netherlands) promotes uptake of ammonia by bacteria in feces and stimulates bowel movement and fecal ammonium removal. Rifaximin (Xifaxan®, Norgine BV, The Netherlands) is an antibiotic that inhibits growth of ammonia-producing bacteria [7]. Ammonia production by the kidney should also be reduced as much as possible. Low potassium levels activate renal ammonia production, and thus, hypokalaemia should be rapidly corrected [9]. Finally, if these measures fail to reduce ammonia levels rapidly, hemodialysis should be considered

In conclusion, non-hepatic hyperammonemia is a rare but severe complication that may occur during treatment of protein malnutrition after bariatric surgery. It is attributed to an acquired urea cycle defect caused by enzyme deficiencies as a result of amino acid depletion. Early recognition and prompt treatment are vital. Protein feeding must be stopped immediately and should be replaced by high-dose intravenous glucose infusion to block ammonia production induced by protein catabolism. When ammonia levels have normalized, low-dose protein feeding should be started slowly to correct the amino acid depletion that may have caused the urea cycle enzyme deficiencies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of report, formal consent is not required.

Informed Consent Informed consent was obtained from the patient described in this report.

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