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Hyperammonemia and Ornithine Transcarbamylase Deficiency after Bariatric Surgery: A Retrospective Study

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Background: The number of bariatric surgeries has risen in the past decades. Hyperammonemia related to ornithine transcarbamylase (OTC) deficiency is a potentially lethal disorder in patients with neurological symptoms. The apparent prevalence of OTC deficiency and potential predictors of mortality was examined in patients after bariatric surgery.
Methods: This is a retrospective study of postoperative patients who developed hyperammonemia in a large, urban teaching hospital. Urinary orotic acid levels were ordered in individuals with elevated plasma ammonia.
Results: Between January 2012 and August 2017, 1597 bariatric surgical procedures were performed. Seven women hospitalized with consistent symptoms had a mean peak plasma ammonia level of 155 umol/L (range: 57 to 273) and mean urinary orotic acid excretion of 3.3 mmol/mol creatinine (range: 1.6–7.9) after vertical sleeve gastrectomy, duodenal switch, or gastric bypass surgery, and there were four mortalities (57%). The apparent postoperative prevalence of OTC deficiency is 0.31%. Peak lactic acid ($p = 0.011$) levels is a predictor of mortality.
Conclusions: Hyperammonemia is associated with a high mortality rate predicted by high lactic acid levels. Postoperative prevalence of OTC deficiency is higher than the general population. Further investigations should examine potential mechanisms for its development.

Keywords: ornithine carbamoyltransferase deficiency disease, hyperammonemia, bariatric surgery, obesity, gastric bypass

Introduction

In response to the ongoing worldwide obesity epidemic, the number of worldwide bariatric surgical procedures continues to increase.[1] The most common bariatric surgical procedures worldwide are the vertical sleeve gastrectomy and the Roux-en-Y gastric bypass,[1] and recognition of post-surgical disorders in these individuals remains an important feature of postoperative care.

The most commonly inherited urea cycle disorder is Ornithine Transcarbamylase (OTC) deficiency (also known as Ornithine Carbamoyltransferase Deficiency), an X-linked recessive disorder. OTC deficiency is caused by decreased activity of the enzyme OTC, which converts carbamoyl phosphate and ornithine into citrulline. Decreased activity of this enzyme disrupts the urea cycle and the removal of nitrogenous waste, resulting in an accumulation of ammonia. Individuals with OTC deficiency will have increased blood ammonia levels as well as increased urinary excretion of orotic acid, but normal blood transaminases and prothrombin time. OTC deficiency was first described in 1962.[2] This disease affects 1 in 8,000 live births in the United States and has an estimated prevalence of 1:14,000–70,000.[3] The clinical presentation of OTC deficiency ranges from coma in neonates to neuropsychiatric disorders in adults. Brassier and associates followed a cohort of 90 patients at a single

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medical center for 40 years to elucidate the long-term characteristics of the disease.[4] In their study, 27 (30%) of the patients diagnosed with OTC deficiency presented in the neonatal period, while 52 (57.8%) patients presented in adolescence (up to age 16). Only 11 (12.2%) patients presented in adulthood, termed late-onset disease. In their study, neonatal presentation carried a mortality of up to 90%, while late onset mortality was 13%. The varying presentation of OTC deficiency is likely due to X chromosome inactivation described in individuals with X-linked recessive traits.

In individuals with OTC deficiency, persistent elevation of ammonia inhibits neurotransmission *via* increased gamma-aminobutyric acid activity, leading to varying levels of altered mental status, lethargy, and coma.[5] Previous reports have identified OTC deficiency in individuals who had undergone Roux-en-Y gastric bypass.[5,6] Since individuals will continue to present with mental status changes after bariatric surgery, this study was designed to examine the apparent prevalence of hyperammonemia related to OTC deficiency and to examine potential predictors of mortality in postoperative bariatric patients.

Materials and Methods

Study population

All procedures performed in studies using human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval for human studies was obtained from the Institutional Human Studies Subcommittee on December 10, 2017. The Human Studies Subcommittee decided that this was a minimal risk protocol and granted a waiver of informed consent for this research study.

This is a single center, retrospective study of patients who underwent bariatric surgery at a single large, urban community teaching hospital between 1999 and 2017. If a patient had macroscopic evidence for cirrhosis at the time of their bariatric surgery, it is a general policy at this medical center that the bariatric surgeon would not proceed to complete the patient's bariatric surgical procedure. Patients who had their original bariatric surgery performed elsewhere but underwent revisional surgery at this medical center were included. Medical records were examined from the medical records department within the medical center and from two electronic medical record systems that are utilized within the medical center and were cross referenced for completeness.

Data collection

For all patients identified with hyperammonemia in this study, the following data were collected: age, sex, weight, height, body mass index, date of surgery, type of bariatric surgery, date of admission, symptoms, plasma ammonia level, urine orotic acid level, lactic acid level, serum chloride, albumin level, reported complications, medical management, liver biopsy results, pathology results, follow-up clinical information, cause of death, and autopsy results.

Statistical analysis

Statistical analysis was performed using SPSS statistics, version 23 (IBM corporation, 1 New Orchard Road, Armonk, New York 10504-1722 United States). Descriptive statistics were calculated for all variables. The independent *t*-test was used for continuous data, which are reported as means with standard deviations. Fisher's exact test was used to examine categorical data (due to the small sample size). Univariate analysis was used to study variables that could be predictive of mortality. A p value of <0.05 is considered to be statistically significant.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author on special request.

Results

Patient population and demographics

Between January 2012 and August 2017, one thousand-five hundred-97 bariatric surgeries were performed. Seven patients were identified who had elevated ammonia levels. In conjunction with elevated excretion of urinary orotic acid, this result provided an apparent postoperative prevalence rate of 0.31% for OTC deficiency. Two of these patients had a sleeve gastrectomy, one patient had a sleeve gastrectomy with revision to a duodenal switch, three patients had Roux-en-Y gastric bypass, and one patient had gastric bypass with revision to a bilio-pancreatic diversion. All patients required hospitalization. All 7 individuals were females, with a mean age of 45 (SD: 11) years (see Table 1). Their mean preoperative body mass index was 45 (SD: 8) kg/m^2, while their mean body mass index at the time of their hospitalization was 31 (SD: 11) kg/m^2. The time from their original surgery to their hospitalization was a mean of 4.3 (SD: 4.4) years. All patients had preoperative evaluation in our bariatric gastroenterology clinic; no patient had a preoperative diagnosis of OTC deficiency and no patient had a known family history of OTC deficiency.

Presentation requiring hospitalization and biochemical findings

Three individuals presented with altered mental status and confusion, one individual in a catatonic state (unresponsive), one individual with nausea and vomiting who developed pulseless electrical activity cardiac arrest, and two individuals with inadequate oral intake and weight loss. None of the seven patients were diagnosed with sepsis at hospital admission.

The mean peak plasma ammonia level was 155 umol/L (SD: 81). The peak plasma ammonia levels ranged from 57 to 273 with a normal range of 11 to 32 umol/L. The mean urinary orotic acid excretion was 3.3 mmol/mol creatinine (SD: 2.4). Urinary orotic acid excretion ranged from 1.6 to 7.9 with a normal range of 0.4 to 1.2 mmol/mol creatinine. Two individuals (one with altered mental status and peak

Table 1. Demographics of Seven Patients with Ornithine Transcarbamylase Deficiency

Characteristic	*Mean*	*SD*
Age	45 Years	11
Preoperative BMI	45 kg/m^2	8
BMI at Hospitalization	31 kg/m^2	11
Time from original surgery to hospitalization	4.3 Years	4.4

ammonia of 150 umol/L and one with confusion, jaundice, and peak ammonia of 164 umol/L) expired before completing a urine collection for orotic acid; at autopsy, neither patient had cirrhosis of the liver. The mean peak lactic acid level was 8.6 nmol/L (SD: 5.6). The peak lactic acid levels ranged from 1.1 to 15 with a normal range of 0.7–2.1 nmol/L. The mean peak chloride level was 116 mmol/L (SD: 4.7). The peak chloride levels ranged from 111 to 126 with a normal range of 98–107 mmol/L. The mean albumin level was 0.24 mmol/L (SD: 0.09). The albumin levels ranged from 0.15 to 0.38 with a normal range of 0.51–0.81 mmol/L. These findings are summarized in Table 2. The individual clinical findings at the time of hospital admission and the final hospital outcomes for each of the seven patients are summarized in Table 3.

Histopathology of liver biopsies

Three individuals underwent liver biopsy. The first individual with a catatonic state (unresponsive) had histopathology that revealed no cirrhosis but chronic portal inflammation with noncaseating granulomas, focal cholestasis, and hepatocyte swelling. The second individual with pulseless electrical activity cardiac arrest had histopathology that revealed no necrosis or bridging fibrosis but minimal chronic venous congestion, minimal centrilobular macrovesicular steatosis, and moderate chronic portal inflammation. The third individual with inadequate oral intake and weight loss had histopathology that revealed minimal chronic portal inflammation and portal fibrosis.

Management and outcomes

These patients were managed with intravenous infusions of thiamine-hydrochloride, oral lactulose, oral Rifaximin, lactulose enemas, and low protein diet.

Of the seven patients, there were four mortalities (57%). The three survivors continued to have evidence for peripheral neuropathy, worsening memory, night vision problems, and vitamin deficiencies upon posthospitalization follow-up. Three individuals underwent postmortem autopsies. The first individual had findings of cardiomegaly, pericardial effusion, and congestive pulmonary edema with focal lung collapse and fibrosis. The second individual had anasarca with hepatomegaly, ascites, macrovesicular steatosis of the liver, pericardial effusion, pleural effusions, and metabolic glia with central pontine myelinolysis. The third individual had anasarca with macrovesicular steatosis, bridging fibrosis and cholestasis, cardiomegaly, bilateral pulmonary congestion with acute pneumonitis, and acute tubular necrosis of the kidneys with glomerulosclerosis.

Predictors of mortality

As shown in Table 4, when comparing survivors with the deceased individuals, there was no statistical difference with regards to mean patient age or mean time between the original bariatric surgery and hospital admission. There was a trend ($p = 0.077$) toward deceased patients have a higher body mass index compared with the surviving patients at the time of admission for hospitalization. When comparing survivors to the deceased individuals, there was no statistical difference with regards to mean peak ammonia, mean urinary orotic acid excretion, mean peak chloride, or mean albumin levels. There was a statistically significant difference ($p = 0.011$) with a higher mean peak lactic acid in deceased individuals compared with surviving patients.

Discussion

The reported prevalence of neurological disorders after bariatric surgery ranges from 5% to as high as 16%.[7,8] In individuals with postbariatric surgery neurological disorders, micronutrient deficiencies should be considered including deficiency of thiamine, cobalamin, copper, zinc, vitamin A, and/or folic acid.[9] In addition, due to the frequent presence of upper gut bacterial overgrowth after bariatric surgery,[10,11] D-lactic acidosis is another potential explanation for neurological symptoms. In individuals with altered mental status and hyperammonemia but normal liver function, the presence of OTC deficiency must be considered after bariatric surgery.

In this present study, the apparent prevalence of postbariatric surgery OTC deficiency was 0.31%, which is significantly >0.007% prevalence of OTC deficiency reported in the general population.[3] All seven of the patients included in this study are women. The clear discrepancy of this disorder affecting females after operative bariatric surgery could be due to OTC deficiency's relationship to an X-linked recessive disorder. Females with an asymptomatic recessive gene could have OTC deficiency unmasked by the triggers of bariatric surgery (body mass index of 40 kg/m^2 or higher, or a body mass index of 35 kg/m^2 to 39.9 kg/m^2 and an obesity-induced medical disorder that is clinically improved following bariatric surgery), macronutrient deficits, and/or micronutrient deficits. The long mean time period (4.3 years) after bariatric surgery suggests that some patients may have developed a somatic gene mutation[12] leading to OTC deficiency or some patients may have altered their ongoing postbariatric surgical program, perhaps due to noncompliance.

The largest case series of hyperammonemia secondary to OTC deficiency has been published by Fenves *et al.*[13] with 20 patients (95% of whom were women) suffering from hyperammonemia syndrome, all of which were after Roux-en-Y gastric bypass. The authors reported that their patients did not have cirrhosis, but did have hypoalbuminemia and low plasma zinc levels. Their reported mortality rate was also high at 50%. Importantly, our present study does report that OTC deficiency can occur after vertical sleeve gastrectomy as

Table 2. Biochemical Findings for 7 Individuals at Hospitalization

Measurement	*Mean*	*SD*	*Range*	*Range of normal*
Peak ammonia	155	81	57–273	11–32 umol/L
Urinary orotic acid excretion	3.3	2.4	1.6–7.9	0.4–1.2 mmol/mol creatinine
Peak lactic acid	8.6	5.6	1.1–15	0.7–2.1 nmol/L
Peak chloride	116	4.7	111–126	98–107 mmol/L
Albumin	0.24	0.9	0.15–0.38	0.51–0.81 mmol/L

Table 3. Summary of Initial Hospitalization Results and Outcomes for seven Patients

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Age at admission	42	51	38	44	48	70	43
Years postop	3.6	0.1	12	1.7	1.5	0.9	10.2
Surgery	VSG	VSG	RYGB	RYGB	RYGB	RYGB	RYGB
Glucose mg/dl	87	99	106	116	116	119	156
Ammonia umol/L	223	89	235	150	57	75	164
Urine orotic acid mmol/mol cr	2.9	7.9	2.1	—	1.6	1.8	—
Lactic acid mmol/L	1.1	15	1.5	11.2	—	14.8	2.1
Liver biopsy	Yes	Yes	—	—	Yes	—	—
Death	No	Yes	No	Yes	No	Yes	Yes
Autopsy	—	Yes	—	Yes	—	—	Yes

well as after Roux-en-Y gastric bypass. This finding suggests that there are similar risk factors after both bariatric surgical procedures, and that the development of appropriate symptoms after vertical sleeve gastrectomy should initiate diagnostic studies to look for evidence of OTC deficiency.

Postoperatively, bariatric surgery patients are instructed on a low fat, high protein diet, and so the postoperative diet might unmask the presence of OTC deficiency. As a potential risk factor for OTC deficiency, there are case reports of high protein diets similarly unmasking OTC deficiency in nonbariatric surgery patients.[14]

In this study, three patients underwent liver biopsy and no patient had evidence for cirrhosis. The risk of cirrhosis in our patient population may be reduced by decisions of our bariatric surgeons to not complete a bariatric surgical procedure in an individual found to have macroscopic evidence for cirrhosis at the time of bariatric surgery. Liver biopsies obtained from both children[15] and an adult[16] with OTC deficiency have revealed only nonspecific changes.

Among potential risk factors for the development of OTC deficiency, there is no evidence from our present study that patient age, time between bariatric surgery and hospital admission, peak ammonia, peak chloride, albumin level, or urinary orotic acid excretion are significant risk factors. There is a trend towards an increased risk of OTC deficiency in individuals with higher body mass index at the time of hospitalization ($p = 0.077$). There is a higher risk of development of OTC deficiency in postbariatric surgery patients with a higher peak lactic acid levels ($p = 0.011$). Lactic acidosis could be the result of multiple underlying disorders[17] including ischemia and thiamine deficiency (patients in this study did receive intravenous infusions of thiamine).

The high mortality in this study may have been a reflection of the late presentations of patients for evaluation of postoperative symptoms. Halting protein intake, providing intravenous glucose and lipids, use of oral or rectal lactulose,[18] and possibly hemodialysis or liver transplantation[19] are current available strategies designed to counteract the risks of hyperammonemia.

Further investigations are required to examine potential mechanisms for the development of OTC deficiency in patients after bariatric surgery. Understanding the mechanisms of development of this disorder could aid clinicians by providing improved preventative measures for postbariatric surgery patients.

Limitations

As a retrospective study, this study has the limitations associated with retrospective studies including an inferior level of evidence when compared with a prospective study. The patient population involves individuals with medically-complicated obesity who decided to undergo bariatric surgery and there was no control group of individuals with medically-complicated obesity who had not undergone bariatric surgery. Not all of the seven patients completed determination of urinary orotic acid excretion or underwent liver biopsy. The small sample size of postbariatric surgery patients who developed OTC deficiency was related to the rarity of this disorder.

Implications

After bariatric surgery, hyperammonemia, which has now been shown to occur after vertical sleeve gastrectomy as

Table 4. Predictors of Mortality

	Surviving individuals	*Deceased individuals*	
	n = *3*	n = *4*	p *value*
Mean [SD] age (Years)	40 [4.8]	48 [14]	0.16
Mean [SD] BMI at admission (kg/m^2)	22 [3.7]	38 [10]	0.077
Mean time [SD] between Bariatric surgery and admission (Years)	5.7 [5.6]	3.2 [4.6]	0.54
Mean peak [SD] ammonia (umol/L)	171 [99]	142 [91]	0.69
Mean [SD] urinary orotic acid excretion (mmol/mol creatinine)	2.2 [0.5]	4.8 [3.0]	0.56
Mean [SD] peak chloride (mmol/L)	114 [2.1]	117 [5.6]	0.59
Mean [SD] albumin (mmol/L)	0.15 [0]	0.28 [0.08]	0.16
Mean [SD] peak lactic acid (nmol/L)	1.3 [0.3]	12.3 [3.2]	0.011

well as after Roux-en-Y gastric bypass, is associated with a high mortality rate of 57%. Mortality may be predicted by high lactic acid levels ($p = 0.011$). The apparent postoperative prevalence of OTC deficiency (0.31%) is higher than that reported in the general population (0.007%). Further investigations are required to examine potential mechanisms for the development of OTC deficiency after bariatric surgery.

Permission for Human Studies

Approval for human studies was obtained from the MedStar Research Institute Human Studies Subcommittee (Columbia, MD) on December 10, 2017.

Authors' Contributions

I.L.P.L.: Conceptualization (lead); formal analysis (lead); writing—original draft (lead). E.W.: Investigation (equal); formal analysis (equal); writing—review and editing (equal). M.S.: Investigation (equal); formal analysis (equal); writing—review and editing (equal). A.L.: Resources (lead). T.R.S.: Conceptualization (equal); writing—review and editing (equal), and T.R.K.: writing—review and editing (equal).

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