

## Fatal Hyperammonemic Encephalopathy After Gastric Bypass Surgery

To the Editor:

The obesity epidemic in the United States has been accompanied by a profound increase in the performance of gastric bypass surgery, a procedure that can cause nutritional deficiencies and metabolic derangements. We recently saw 5 women who had no history of liver disease and who developed fatal hyperammonemic encephalopathy after Roux-en-Y gastric bypass surgery for morbid obesity (Table 1). All patients presented with altered mental status, and none had central nervous system lesions by computed tomography. There were no histories of substance abuse or the use of medications that interfere with the urea cycle. All patients had evidence of nutritional deficiency with hypoalbuminemia, and all had hypoglycemia documented at least once during the hospitalization. Analysis of the ornithine transcarbamylase gene in 2 patients revealed no mutations. All patients eventually lapsed into coma and died despite treatment with lactulose, antibiotics, nutritional repletion, and supportive care.

The cause of this virulent syndrome is not clear. None of our patients had a history of liver disease, and liver biopsies in 3 patients revealed no disease of sufficient severity to cause hepatic failure. Our patients seem to have acquired a disorder of the urea cycle, the essential pathway for the disposal of ammonia.

Requests for reprints should be addressed to Andrew Fenves, MD, 3601 Swiss Avenue, Dallas, TX 75204.  
E-mail address: fenvesa@dneph.com

Encephalopathy has been described as a rare complication of gastric bypass surgery, but it generally has been attributed to deficiencies of thiamine and other nutrients.<sup>1</sup> Recently, there was a report of a 29-year-old woman who developed hyperammonemic encephalopathy after bariatric surgery.<sup>2</sup> DNA analysis revealed no coding mutations in the ornithine transcarbamylase gene, but functional enzymatic testing using fresh-frozen liver tissue revealed less than 1% of normal ornithine transcarbamylase activity. Whereas ornithine transcarbamylase deficiency is an X-linked disorder, and female carriers of 1 mutant gene can remain asymptomatic indefinitely, the authors suggested that their patient was such a carrier whose subclinical disease somehow became manifest after bariatric surgery.

No ornithine transcarbamylase gene mutations are found by DNA analysis in 20% to 30% of patients with ornithine transcarbamylase deficiency,<sup>3</sup> and so it is possible that our patients were asymptomatic carriers of an X-linked, abnormal ornithine transcarbamylase gene. It is interesting that all of our patients had at least 1 documented episode of hypoglycemia. Gastric bypass has been reported to result in hyperinsulinemia with hypoglycemia caused by nesidioblastosis,<sup>4</sup> and insulin can downregulate the expression of urea cycle enzymes by hepatocytes.<sup>5</sup> Zinc deficiency also can interfere with ornithine transcarbamylase function.<sup>6</sup> It is conceivable that a combination of hyperinsulinemia and zinc deficiency brought on by gastric bypass may have contributed to unmask ornithine transcarbamylase deficiency in our patients, but further studies are needed to establish the mechanisms underlying their hyperammonemic encephalopathy.

**Table 1** Clinical Data on Patients with Fatal Hyperammonemic Encephalopathy After Gastric Bypass Surgery

Age (y)	Sex	Years Since Bypass	Albumin* (g/dL)	ALT* (U/L)	Bilirubin* (mg/dL)	Peak Ammonia (μg/dL)	Hypoglycemia During Hospitalization	Liver Biopsy Results
50	F	1.4	2.0	43	1.0	234	Yes	NA
48	F	0.3	2.0	58	5.0	86	Yes	Steatosis, no cirrhosis, mild inflammation
26	F	1.4	1.3	26	0.8	486	Yes	Steatosis, no cirrhosis, moderate inflammation
58	F	28	1.5	66	1.6	76	Yes	NA
41	F	6	2.1	29	7.0	68	Yes	Steatosis, no cirrhosis, mild inflammation

ALT = alanine aminotransferase; NA = not available.

\*Values at time of hospital admission.

We think it is important to make clinicians aware of this syndrome so that it can be recognized early, thereby enabling the performance of appropriate tests to elucidate the underlying mechanisms and to implement therapy that might prevent the fatal outcome.

Andrew Fenves, MD

C. Richard Boland, MD

Rita Lepe, MD

Paulino Rivera-Torres, MD

*Department of Internal*

*Medicine, and the Baylor Charles A. Sammons Cancer Center*

*Baylor University Medical Center*

*Dallas, Tex.*

Stuart Jon Spechler, MD

*Division of Gastroenterology, Department of Internal Medicine*

*Dallas VA Medical Center, and UT Southwestern Medical*

*Center at Dallas, Dallas, Tex.*

doi:10.1016/j.amjmed.2007.08.032

## References

1. Juhasz-Pocsine K, Rudnicki SA, Archer RL, Harik SI. Neurologic complications of gastric bypass surgery for morbid obesity. *Neurology*. 2007;68:1843-1850.
2. Hu WT, Kantarci OH, Merritt JL 2nd, et al. Ornithine transcarbamylase deficiency presenting as encephalopathy during adulthood following bariatric surgery. *Arch Neurol*. 2007;64:126-128.
3. Yamaguchi S, Brailey LL, Morizono H, et al. Mutations and polymorphisms in the human ornithine transcarbamylase (OTC) gene. *Hum Mutat*. 2006;27:626-632.
4. Service FJ, Thompson GB, Service FJ, et al. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N Engl J Med*. 2005;353:249-254.
5. Li Z, Yarmush ML, Chan C. Insulin concentration during preconditioning mediates the regulation of urea synthesis during exposure to amino acid-supplemented plasma. *Tissue Eng*. 2004;10:1737-1746.
6. Aquilio E, Spagnoli R, Riggio D, Seri S. Effects of zinc on hepatic ornithine transcarbamylase (OTC) activity. *J Trace Elem Electrolytes Health Dis*. 1993;7:240-241.