CLINICAL PROBLEM-SOLVING

At a Loss

Joseph F. Merola, M.D., Paiman Peter Ghoroghchian, M.D., Ph.D., Martin A. Samuels, M.D., Bruce D. Levy, M.D., and Joseph Loscalzo, M.D., Ph.D.

In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

A 31-year-old woman who had been unable to eat or drink for the preceding week was admitted to the hospital. For the preceding 8 months she had had nausea, vomiting, and abdominal discomfort and several episodes of crampy epigastric pain with vomiting and intermittent chills and sweats, but no documented fevers. She also had loose, pale stools occasionally, but these episodes did not represent a notable change from her baseline. Gradually increasing fatigue, loss of appetite, and a recent weight loss of several kilograms were also reported.

The patient's medical history included hypertension, obesity, and migraine headaches. She had undergone Roux-en-Y gastric bypass 5 years before presentation and subsequently lost approximately 45 kg (100 lb). Her weight had been stable for the past few years; her body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) was 33. She had undergone laparoscopic cholecystectomy 10 years before presentation. Her only medication was nifedipine, and she took a multivitamin on occasion.

From the Clinical Pathological Conference Series, Departments of Medicine (J.F.M., P.P.G., B.D.L., J.L.) and Neurology (M.A.S.), Brigham and Women's Hospital and Harvard Medical School, Boston. Address reprint requests to Dr. Levy at Brigham and Women's Hospital, Harvard Institutes of Medicine Bldg. (HIM855), 77 Ave. Louis Pasteur, Boston, MA 02115, or at blevy@partners.org.

Drs. Merola and Ghoroghchian contributed equally to this article.

N Engl J Med 2012;367:67-72.
DOI: 10.1056/NEJMcps1111668

An Interactive Medical Case related to this Clinical Problem-Solving article is available at NEJM.org

The increase in the number and severity of symptoms during the previous 8 months suggests a serious disorder, and the gastric bypass surgery raises important issues for consideration. The differential diagnosis at this point is broad and includes disorders of the gastrointestinal tract, liver, and pancreas as well as complications related to the patient's abdominal surgeries. Nausea and vomiting often occur soon after Roux-en-Y gastric bypass, but when the symptoms develop several years after surgery, the differential diagnosis should include bowel obstruction from strictures or adhesions, anastomotic ulcers adjacent to the gastric attachment site, and nutritional deficiencies from malabsorption or bacterial overgrowth. Additional questioning is indicated to assess the possibility of a central cause of vomiting (e.g., increased intracranial pressure); however, most neurologic causes of vomiting are not associated with nausea.

The patient had been laid off from her job the previous year. She had smoked approximately one pack of cigarettes per day for 15 years and reported minimal alcohol use. She was a single mother of two children and had not been sexually active for several years. A review of systems was notable for new headaches associated with the onset of nausea and vomiting. The headaches were constant, dull, not localized to any particular region, and unlike her typical migraine headaches. She also noted the development of increasing numbness and tingling sensations in both hands and feet over the past 3 months and reported having difficulty walking over the past month.

Migraine headaches may be associated with episodic nausea and vomiting and with paresthesias; however, on presentation, this patient described the new headaches

as being different from her typical migraines. The tingling in her feet suggests the possibility of peripheral neuropathy, which rarely results from cobalamin (vitamin B_{12}) deficiency alone but can occur with deficiencies of multiple B vitamins or with copper deficiency. The patient's history of gastric bypass surgery puts her at risk for malabsorption and for deficiencies of vitamins and other nutrients, particularly iron, B vitamins, vitamin D, vitamin E, zinc, copper, and essential fatty acids. Her history of obesity increases the risk of diabetes and its complications (including gastroparesis and neuropathy); however, weight loss after bariatric surgery should decrease the risk of diabetes. Spinal cord disorders could be the source of the symptoms in her legs and feet.

On examination, the patient was afebrile; her pulse was 115 beats per minute, her blood pressure 184/119 mm Hg, and her respiratory rate 14 breaths per minute. There was no jugular venous distention. The findings on cardiovascular and pulmonary examinations were otherwise within normal limits. Slight epigastric tenderness on palpation was present without rebound or guarding. Sensation of light touch was decreased from her toes to just below her knees, sensation of vibration was absent at her toes and decreased at her ankles, and deep-tendon reflexes were diminished at both the knees and the ankles. Her toes were downgoing in response to plantar stimulation.

The patient continued to have intractable nausea and vomiting in the emergency department. Intravenous fluids were administered (1 liter of 0.90% sodium chloride followed by a continuous infusion of 5% dextrose in a solution of 0.45% sodium chloride). She was admitted to the hospital for further evaluation and management of care.

The hematocrit was 29.4%, with a mean corpuscular volume of 109 fl. The white-cell count was 9350 per cubic millimeter and her platelet count 432,000 per cubic millimeter. The aspartate aminotransferase level was 210 U per liter, alanine aminotransferase 44 U per liter, alkaline phosphatase 191 U per liter, total bilirubin 0.6 mg per deciliter (10.3 μmol per liter), albumin 3.3 g per deciliter, prothrombin time 13.6 seconds, and partial-thromboplastin time 33.8 seconds. Amylase and lipase levels were normal, and a serum test for beta human chorionic gonadotropin was negative. Abdominal computed tomography revealed a diffusely fatty liver, with focal sparing of the medial portion of the right lobe, and hepatomegaly, with a liver span of 26.5 cm; the spleen, measuring 14.2 cm, showed borderline enlargement. There were no enlarged lymph nodes, and the pancreas appeared normal. The patient's gallbladder had been removed, and she had undergone gastric bypass with antegastric, antecolic Roux-en-Y gastrojejunostomy and distal enteroenterostomy; the appearance of the excluded portion of the stomach was unremarkable.

There is no evidence of heart failure, but the patient's blood pressure is inadequately controlled by the prescribed nifedipine, and her elevated blood pressure, together with the intractable nausea and vomiting, may have a neurologic cause. It is important to establish whether she has been taking her medication as prescribed.

The elevation in the aspartate aminotransferase level without a concomitant increase in the alanine aminotransferase level suggests that the former may be of muscular origin, although this pattern may also be seen in association with alcoholic fatty liver disease. The macrocytic anemia suggests the possibility of folate or cobalamin deficiency; the patient is at particular risk for both, given her history of gastric bypass surgery. In addition, chronic alcohol use with associated malnutrition can lead to macrocytosis. Copper deficiency can also lead to anemia, but the anemia is typically microcytic, a result of associated iron deficiency.

On the second hospital day, confusion, blurry vision, and vertigo developed abruptly. A repeat examination revealed impaired lateral gaze in both eyes and nystagmus on both horizontal and upward gaze, with a positive Romberg test. The patient was noted to have a wide-based, unsteady gait and was able to take only a few steps, with assistance from two people. She gave vague responses to questions for which she would be expected to know the answer (e.g., describing her children). The patient recalled nothing about a simple story when questioned 5 minutes after hearing it. She did not remember the physicians who had been caring for her and repeatedly asked the same questions of hospital staff at intervals of approximately 15 minutes.

The abrupt and dramatic development of ataxia, oculomotor dysfunction, and encephalopathy is typical in patients with Wernicke's encephalopathy that is caused by a deficiency of thiamine

(vitamin B_1). Thiamine deficiency can also be manifested as acute encephalopathy. This patient's amnestic state rules out a sole finding of myelopathy (e.g., transverse myelitis), myeloneuropathy (e.g., copper deficiency), or neuropathy (e.g., diabetes or chronic alcohol exposure). The findings of reduced reflexes and length-dependent sensory loss in the legs are inconsistent with a pure encephalopathy (e.g., infectious or paraneoplastic limbic encephalopathy) or encephalomyelopathy (e.g., cobalamin deficiency). Giving patients with thiamine deficiency glucose before administering thiamine, as was done in the treatment of this patient, can precipitate or worsen Wernicke's encephalopathy. Parenteral thiamine should be administered immediately and, in general, before the administration of glucose.

The patient was given 500 mg of thiamine intravenously on an emergency basis. Subsequent testing revealed low levels of whole-blood thiamine (45 nmol per liter; normal range, 80 to 150) and of serum folate (4.6 ng per milliliter [10.4 nmol per liter]; normal range, 5.3 to 9.9 ng per milliliter [12.0 to 22.4 nmol per liter]), copper (46 μg per deciliter [7.2 μmol per liter]; normal range, 80 to 155 μg per deciliter [12.6 to 24.4 μmol per liter]), zinc (57 μg per deciliter [8.7 μmol per liter]; normal range, 66 to 120 μg per deciliter [10.0 to 18.4 μmol per liter]), and 25-hydroxyvitamin D (6 ng per milliliter [15 nmol per liter]; normal range, 25 to 80 ng per milliliter [62 to 200 nmol per liter]). Levels of cobalamin and methylmalonic acid were normal. Serum and urine toxicology screens were normal, and the level of serum ammonia and the results of protein electrophoresis and rapid plasma reagin testing were within normal limits.

The patient's thiamine deficiency is probably attributable to malabsorption resulting from the Roux-en-Y gastric bypass, in which a segment of the small intestine is circumvented; bacterial overgrowth of the small intestine, which may also occur after this surgery, could be another cause. Deficiencies of vitamin D, copper, and zinc are also known to occur after gastric bypass surgery, as is cobalamin deficiency, although this patient does not have cobalamin deficiency. To prevent the development of nutrient deficiencies, dietary supplementation with essential vitamins and minerals is required after gastric bypass. Because administration of thiamine has few adverse effects and several of the complications of thiamine deficiency are irreversible, intravenous thiamine was administered in this patient on an emergency basis.

Electromyography was performed to evaluate the peripheral neuropathy noted on presentation, and the results suggested a generalized, length-dependent polyneuropathy with prominent involvement of sensory axons but no electrophysiological evidence of a demyelinating polyneuropathy. Magnetic resonance imaging of the brain showed enhancement and enlargement of the mammillary bodies (Fig. 1), indicating necrosis and confirming the diagnosis of Wernicke's encephalopathy.

The results of both these diagnostic tests are consistent with the diagnosis of Wernicke's encephalopathy. Given the patient's typical clinical presentation, however, these studies would not be required to establish the diagnosis unless the patient did not have a prompt response to the administration of parenteral thiamine.

The patient's headache, nausea, vomiting, oculomotor dysfunction, ataxia, and memory impairment abated on administration of 500 mg of thiamine intravenously three times per day for 2 days, then daily for 7 days. To address the additional nutrient deficiencies, the patient was given intravenous copper and oral zinc, folate, cyanocobalamin, and ergocalciferol, as well as a daily multivitamin.

The patient subsequently reported having had depression for the previous several months and amended her initial report of "minimal" alcohol use, stating that she had engaged in binge drinking over the previous several weeks. She also said that she had not taken nifedipine or the recommended bariatric nutritional supplements routinely. Her blood pressure improved after treatment with nifedipine was restarted and with the addition of lisinopril. A psychiatric consultation was scheduled for soon after discharge to assist in the management of depression, discontinuation of unhealthy alcohol use, and adherence to the regimen for medication and nutritional supplementation. She was discharged home on daily supplementation with 100 mg of oral thiamine in addition to copper, cyanocobalamin, ergocalciferol, folic acid, a multivitamin, zinc sulfate, and magnesium gluconate.

Six weeks after hospital discharge, the patient had improvement in short-term memory, normal

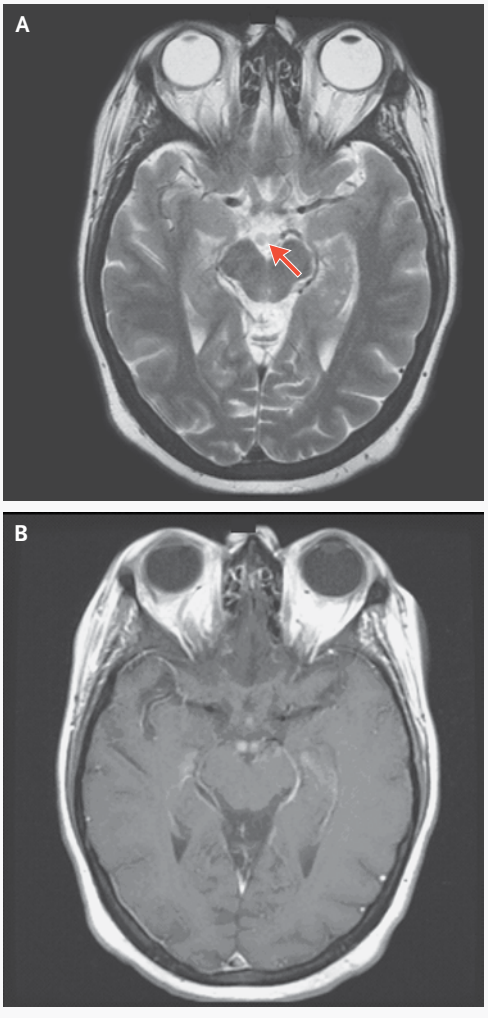

Figure 1. Axial Images of the Brain.

Enlargement of the mammillary bodies is shown in an image obtained with fluid-attenuated inversion recovery sequencing (Panel A, arrow), and enhancement is shown in a T_1-weighted magnetic resonance image obtained after the administration of contrast material (Panel B).

language function, and normal eye movement, with the exception of mild impairment of left eye adduction and a rotatory nystagmus on leftward gaze.

DISCUSSION

In the 1880s, Carl Wernicke first described hemorrhagic changes in the gray matter of the mammillary bodies in three patients with alcoholism, a condition that he called polioencephalitis hemorrhagica superior, and Sergei Korsakoff independently described a "polyneuritic amnestic syndrome" in 18 patients with alcoholism.[1-4] In a large clinical study performed by Victor and colleagues at Boston City Hospital in the 1950s, Wernicke's encephalopathy was described as an encephaloneuropathic syndrome consisting of changes in mental status (confusion, confabulation, short-term memory loss, and psychosis), ocular dysfunction (nystagmus, gaze palsies, and ophthalmoplegia), and gait ataxia.[5] Usually beginning with double vision, dysarthria, ataxia, and paresthesias of the legs, Wernicke's encephalopathy can rapidly progress to Korsakoff's syndrome, which is characterized by anterograde and retrograde amnesia, confabulation, meager content in conversation, lack of insight, and apathy. With repeated or severe attacks of Wernicke's encephalopathy, the neurologic abnormalities may become irreversible. Therefore, the condition must be viewed as a medical emergency requiring prompt treatment with parenteral thiamine, and efforts should be made to prevent its occurrence by providing thiamine supplementation in patients recognized to be at high risk for deficiency.

Although Wernicke's encephalopathy is typically observed in malnourished patients with alcoholism, clinically significant thiamine deficiency, which may lead to heart failure, can also develop in patients with chronic gastritis or Crohn's disease, in patients with repetitive vomiting resulting from chemotherapy, and in those who have undergone bariatric surgery. In some patients with thiamine deficiency, plasma thiamine levels are normal; thus, measurement of the more sensitive whole-blood thiamine level is necessary to confirm the diagnosis. In rare situations, measurement of the thiamine diphosphate level or erythrocyte thiamine transketolase activity is necessary for diagnosis. The case presented here highlights the increased risk of deficiencies of thiamine and other nutrients in patients after gastric bypass surgery,[6] especially when, as in this patient, there is concomitant alcohol use and prolonged nausea and vomiting.

There should be a low threshold for thiamine administration to prevent heart failure and Wernicke's encephalopathy in patients at risk for deficiency or in those with symptoms that may be the result of deficiency; intravenous thiamine

is safe, and the administration of glucose without thiamine can precipitate or worsen Wernicke's encephalopathy. Prophylactic thiamine administration would have been a reasonable approach to the treatment of this patient, given her vomiting and history of gastric bypass surgery, and would probably have prevented the worsening of her condition in the hospital. Because the absorption of oral thiamine is erratic, parenteral thiamine, as administered in this case, should be used to treat clinically significant thiamine deficiency.[7] Data from randomized trials are lacking to inform the optimal dosing regimen; however, clinically significant thiamine deficiency is typically treated with at least 200 mg of parenteral thiamine daily for 2 days,[7] with some experts recommending 500 mg three times daily for 2 days, followed by 500 mg once daily for 5 days.[8] On completion of parenteral treatment, the patient should take an oral thiamine supplement daily.

With the increasing prevalence of obesity in the United States, bariatric surgeries are being performed more frequently.[6] There are two major categories of bariatric procedures: malabsorptive (in which food is made to bypass a large segment of the intestine) and restrictive (in which staples or an adjustable gastric band is used to limit the amount of food that can be accommodated in the stomach). The Roux-en-Y gastric bypass procedure is an example of a combined malabsorptive and restrictive approach that involves stapling the stomach to form a small pouch while also bypassing part of the intestine (Fig. 2).

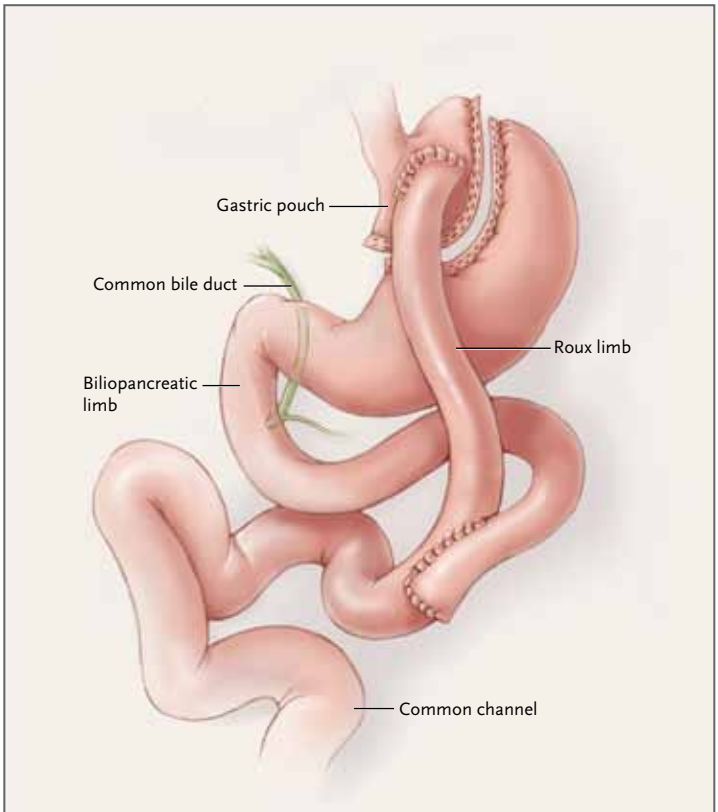

Figure 2. Roux-en-Y Gastric Bypass.

The Roux-en-Y gastric bypass is a procedure used for the treatment of morbid obesity that combines restrictive and malabsorptive approaches. The stomach is stapled to create a small gastric pouch, and the small intestine is divided at the midjejunum. The gastric pouch is anastomosed to the distal portion of the jejunum (Roux limb), and the distal stomach and proximal portions of the jejunum (biliopancreatic limb) are anastomosed farther down the jejunum to create a common channel.

Gastric bypass surgery puts patients at a much higher risk of nutritional deficiencies than does gastric band surgery because food bypasses the duodenum, compromising the absorption of vitamins and minerals. In addition to thiamine deficiency, this patient had deficiencies of copper, zinc, folate, and vitamin D. Copper deficiency causes a myeloneuropathy without an encephalopathy,[9,10] and this condition can be clinically similar to the subacute combined degeneration of the posterior and lateral columns of the spinal cord that is seen in cobalamin deficiency. Because the patient was symptomatic, with a polyneuropathy, copper was administered intravenously to allow for more rapid correction; however, copper deficiency can also be treated with oral supplementation. Serum levels of copper and zinc should be followed closely when oral replacement of copper is used, especially in patients who are also receiving a supplement for zinc deficiency, because zinc and copper compete for intestinal absorption.

Given the postoperative risk of profound vitamin and mineral deficiencies, patients who have undergone bariatric surgery should have close follow-up with a bariatric dietitian and should understand the importance of adherence to postoperative vitamin and mineral supplementation, including daily intake of calcium, vitamin D, cyanocobalamin, and a multivitamin that includes iron, folic acid, copper, zinc, and thiamine.[11-13] This case highlights the risks of nonadherence to supplementation regimens and the need for physicians to consider vitamin and mineral defi-

ciencies in patients who present with symptoms after bariatric surgery, especially when those symptoms are otherwise unexplained.

Dr. Samuels reports receiving salary support and payment for educational presentations from Lighthouse Learning and royalties from Oakstone Publishing, McGraw-Hill, and Elsevier. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Die acute, häemorrhagische Polioencephalitis superior. In: Wernicke C. Lehrbuch der Gehirnkrankheiten fur Aerzte und Studirende. Vol. 2. Berlin: Verlag von Throdor Fischer, 1881:229-42.
2. Korsakoff SS. Disturbance of psychic function in alcoholic paralysis and its relation to the disturbance of the psychic sphere in multiple neuritis of non-alcoholic origin (1887). In: Victor M, Adams RD, Collins GH. The Wernicke–Korsakoff syndrome. Contemporary neurology series. Oxford, United Kingdom: Blackwell, 1971.
3. Victor M, Yakovlev PI. S.S. Korsakoff's psychic disorder in conjunction with peripheral neuritis: a translation of Korsakoff's original article with comments on the author and his contribution to clinical medicine. Neurology 1955;5:394-406.
4. Korsakoff SS. Etude médico-psychologique sur une forme des maladies de la mémoire. Revue Philosophiquee 1889;20:501-30.
5. Victor M, Adams RD, Collins GH. The Wernicke-Korsakoff syndrome: a clinical and pathological study of 245 patients, 82 with post-mortem examinations. Contemp Neurol Ser 1971;7:1-206.
6. DeMaria EJ. Bariatric surgery for morbid obesity. N Engl J Med 2007;356:2176-83.
7. Day E, Bentham P, Callaghan R, Kuruvilla T, George S. Thiamine for Wernicke-Korsakoff syndrome in people at risk from alcohol abuse. Cochrane Database Syst Rev 2004;1;CD004033.
8. Thomson AD, Cook CCH, Touquet R, Henry JA. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and emergency department. Alcohol Alcohol 2002;37:513-21. [Erratum, Alcohol Alcohol 2003;38:291.]
9. Kumar N. Neurologic presentations of nutritional deficiencies. Neurol Clin 2010;28:107-70.
10. Kumar N, McEvoy KM, Ahlskog JE. Myelopathy due to copper deficiency following gastrointestinal surgery. Arch Neurol 2003;60:1782-5.
11. Furtado LC. Nutritional management after Roux-en-Y gastric bypass. Br J Nurs 2010;19:428-36.
12. Shankar P, Boylan M, Sriram K. Micronutrient deficiencies after bariatric surgery. Nutrition 2010;26:1031-7.
13. Frank P, Crookes PF. Short- and long-term surgical follow-up of the postbariatric surgery patient. Gastroenterol Clin North Am 2010;39:135-46.

CLINICAL PROBLEM-SOLVING SERIES

The *Journal* welcomes submissions of manuscripts for the Clinical Problem-Solving series. This regular feature considers the step-by-step process of clinical decision making. For more information, please see authors.NEJM.org.