Wernicke Encephalopathy Owing to Vitamin Nonadherence Following Bariatric Surgery

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ABSTRACT

Introduction and Objective
Wernicke encephalopathy (WE) is increasingly recognized as a complication of bariatric surgery precipitated by nonadherence to vitamin supplementation in the setting of presurgical hypovitaminosis, nausea, vomiting, gastrointestinal dysmotility, and the high cost of vitamins. Anticipation of this phenomenon allows prompt diagnosis and treatment, which can prevent serious neurologic morbidity and even death.

Case Presentation
We present a patient with prominent neuro-ophthalmic manifestations of Wernicke encephalopathy from medication nonadherence owing to a combination of factors: the high cost of vitamin supplements, nausea, and depression.

Discussion
Wernicke encephalopathy after bariatric surgery is likely to become more common as these procedures increase in frequency. Physicians should recognize the factors that lead to medication nonadherence in this context and anticipate the development of Wernicke encephalopathy, as early recognition is critical to prevent enduring neurologic deficits.

Conclusion
Anticipation of this phenomenon allows prompt diagnosis and treatment, which can prevent serious neurologic morbidity and even death.

Introduction
Wernicke encephalopathy (WE), a neurologic condition precipitated by thiamine (vitamin B1) deficiency, manifests with some combination of acute cognitive impairment, ataxia, gaze palsies, and nystagmus. Early diagnosis can be lifesaving.1
Although thiamine deficiency is traditionally associated with alcoholism, it has been increasingly reported after bariatric surgery. Nearly half a million bariatric operations were performed worldwide in 2013. In the United States, the number of bariatric surgeries rose nearly 10% between 2013 and 2015, from 179,000 to 196,000. Thus, while the overall incidence of WE following bariatric surgery is low, the rapid rise in bariatric operations makes it an important setting for WE. Patients who undergo bariatric surgery are vulnerable to WE from nonadherence to nutritional supplements, nausea and vomiting, and low thiamine levels before surgery.

The required lifelong vitamin supplementation can be expensive and burdensome. For example, the supplement regimen after Roux-en-Y gastric bypass surgery includes multiple daily doses of multivitamins (containing thiamine), calcium, vitamin D, vitamin B12, iron, and vitamin C.

We present a patient who developed postbariatric WE owing to medication nonadherence in order to highlight the risk factors for this phenomenon. To our knowledge, this is the first case report in which the high cost of postbariatric vitamin supplementation contributed to vitamin nonadherence and ultimately WE.

**Case Presentation**

A 34-year-old woman who had undergone Roux-en-Y gastric bypass surgery 11 months earlier presented with 8 months of progressive bilateral leg weakness and three weeks of diplopia. Her oral intake had declined 2 to 3 months after bariatric surgery because of persistent nausea and intermittent vomiting. In the weeks prior to presentation, she had become dependent on a walker and had experienced dysesthesias in her arms and legs. At that time, she also developed episodic binocular horizontal diplopia.

The patient’s past medical history was notable for bipolar disorder with a prior hospitalization following a suicide attempt in the year before her bariatric surgery. Other past medical history included anxiety, asthma, GERD, migraines, and hyperlipidemia.

Her home medications included buspirone, fluoxetine, lurasidone, trazodone, propranolol, topiramate, meclizine, hydrocodone-acetaminophen, omeprazole, ondansetron, albuterol, budesonide-formoterol, montelukast, atorvastatin, loratadine, and fluticasone. While she was prescribed postbariatric vitamin and mineral supplementation, she reported that she had not filled the prescriptions because “they were too expensive.” Allergies and family history were noncontributory. Social history included spousal violence.

In the emergency room, the patient’s mental status was normal except for a flat affect. She had bilateral abduction deficits and esotropia in all gaze positions. Horizontal saccades were slow in both eyes but vertical saccades were of normal velocity. She had a right-beating nystagmus in right gaze, a left-beating nystagmus in left gaze, and an upbeat nystagmus in upgaze. Upper extremity strength was 4/5 throughout. Lower extremity strength was 1/5 throughout. She reported no vibratory sense in the lower extremities. Deep tendon reflexes were 2+ in the upper extremities and absent in the lower extremities.

Complete blood count and basic metabolic panel were normal. Serum thiamine was low at < 7 nmol/L (normal range is 8–30 nmol/L). Folate, copper, zinc, B12, and methylmalonic acid levels were normal.

Brain and full spine MRI was normal. Nerve conduction and electromyography studies showed a severe sensory-predominant axonal polyneuropathy.

In summary, ophthalmologic findings included horizontal saccadic slowing, bilateral abduction deficits, side-beat nystagmus, and upbeat nystagmus. Neurologic findings included profound bilateral lower extremity weakness and distal sensory loss, distal areflexia, and laboratory evidence of axonal polyneuropathy.

She received thiamine 500 mg per day intravenously for 3 days, followed by thiamine 100 mg per day orally. The abduction deficits resolved.
completely within 48 hours, but the nystagmus persisted (Video 1: https://quod.lib.umich.edu/m/mjm/images/13761231.003.111-00000001.wmv). The lower extremity weakness gradually improved. Upon discharge approximately 3 weeks after presentation, she displayed mild bilateral hip flexor weakness but otherwise intact strength in her lower extremities. Even with assistance, she was only able to ambulate 5 feet. Thereafter, she was lost to follow-up.

Discussion

Our patient developed WE because she was nonadherent to nutritional therapy following bariatric surgery. Her noncompliance with vitamin supplementation compounded the risk of thiamine deficiency from chronic vomiting and obesity-related nutritional deficiencies.6,7,8,9

Thiamine deficiency probably arises from a combination of vomiting, limited oral intake, poor digestion, and malabsorption.7 It is more common after predominantly malabsorptive procedures, such as biliopancreatic diversion, yet it may also occur following predominantly restrictive procedures, such as vertical banded gastroplasty,12 sleeve gastrectomy, and gastric bypass, especially if persistent vomiting is present.13 Surgical complications that cause vomiting, such as anastomotic or gastric sleeve stenosis, dumping syndrome, or gastrointestinal motility disorders, may predispose to thiamine deficiency. Preexisting obesity also contributes to micronutrient deficiencies independent of bariatric surgery.11 One study found that 15% of obese patients were deficient in thiamine prior to surgery.6

Nonadherence to vitamin supplements after bariatric surgery in adults may exceed 50%,14 and is even higher in adolescents.15 In our patient, nonadherence was principally due to the high cost of the vitamins and chronic nausea. Because vitamin supplementation after bariatric surgery must be maintained indefinitely, cost may be a major impediment. Two years after gastric bypass surgery, Swiss patients spent an average of $35 a month for nutritional supplements alone.16 In the United States, health insurance rarely covers vitamin and mineral supplementation.17

A mood disorder may have contributed to nonadherence in our patient. Morbid obesity is associated with multiple psychopathological conditions that can impact postsurgical outcomes,18 and psychopathology has been linked to vitamin nonadherence.19-20

The incidence of WE following bariatric surgery is unclear. A systematic review found it in 0.2% of patients following predominantly malabsorptive bariatric operations.5 Another study found a less than 0.5% incidence of micronutrient-responsive cerebral dysfunction, mostly resembling WE, following restrictive and malabsorptive surgeries.4

Predicting which patients with thiamine deficiency will progress to WE is difficult. WE probably arises from a complex interplay of factors such as genetic predisposition, folic acid deficiency, malnutrition, diarrhea, vomiting, liver disease, diuretic therapy, magnesium levels, and coexisting systemic disease.21 Given the pathologic complexity, the incidence and latency of developing WE will vary. In a 1947 series from a Singapore prisoner-of-war hospital, prisoners did not develop WE until 6 weeks after starting a thiamine-deficient diet.22 Although some patients have reportedly developed WE as soon as 2 weeks following bariatric surgery,23 most patients develop it after 4 to 12 weeks,24 and a minority of patients develop it more than 12 weeks after surgery.5

As reported in more than 80% of alcoholic patients, the principal oculomotor manifestations of WE are nystagmus, horizontal gaze palsy, and abduction deficits.25 In a systematic review of 84 patients with bariatric WE, 83% had nystagmus or gaze palsy.5 Gaze palsies likely result from lesions in the pontine tegmentum and abducens and oculomotor nuclei.1 Additionally, side-beat nystagmus is often noted.1,26-27

Ophthalmoscopic abnormalities are uncommon in patients with alcoholic and bariatric surgery-associated WE. Wernicke described one
case of bilateral optic neuritis with edema and hemorrhages and one case with optic disc hyperemia. In a 1971 review of 245 alcoholic patients, 2% had retinal hemorrhages, and none had optic disc edema. Only 3 of 84 patients in one review of bariatric WE had peripapillary or retinal hemorrhages; all 3 had coexisting papilledema, and 1 had papilledema without hemorrhages. Optic disc edema and pallor and peripapillary hemorrhages have also been documented in WE in gastrointestinal illness, hyperemesis gravidarum, childhood malnourishment, and chronic diarrhea. Alcoholic WE is more often associated with central and cecocentral scotomas, subnormal visual acuity, and pale optic discs, abnormalities that have rarely been described in bariatric WE.

The similarities between the ophthalmoscopic abnormalities described in alcoholic and bariatric WE and those in methanol-induced optic neuropathy and Leber hereditary optic neuropathy have prompted the hypothesis that mitochondrial dysfunction plays a pathogenetic role. In a case of alcoholic WE with refractory optic neuropathy, a DNA mutation identifying underlying Leber hereditary optic neuropathy was reported.

Recognizing the ophthalmic manifestations is critical to the diagnosis of WE. Although the syndrome of mental status changes, gait ataxia, abduction deficits, and nystagmus is classic, a significant proportion of patients exhibit only 1 or 2 of these findings. In bariatric surgery studies, the full clinical syndrome has been present in 25% to 66% of patients. In a study of WE in 131 alcoholics, the classic syndrome appeared in only 16% of patients and was only 22% sensitive. Diagnostic sensitivity increases to 85% when 2 of the following criteria are present: oculomotor abnormalities, dietary deficiency, cerebellar dysfunction, and altered mental status or memory impairment. Such expanded criteria can be applied to nonalcoholic patients as well.

Laboratory confirmation of thiamine deficiency is not required for the diagnosis of WE. Whole blood thiamine is the preferred assay, but thiamine levels are often normal in WE because blood levels do not adequately reflect brain thiamine levels. Blood samples should be drawn before thiamine supplementation is provided, as laboratory abnormalities quickly return to normal with treatment. Moreover, the results of this specialized laboratory test are often delayed. In our patient, the treating team received the low thiamine result 11 days after it was ordered. Because delays may adversely affect clinical outcome, treatment should be initiated presumptively.

Brain imaging abnormalities are also not required for diagnosis. Typical brain MRI findings include hyperintense T2 signals in the dorsal medial thalamic nuclei periaqueductal gray area, and at the borders of the third and fourth ventricles. These abnormalities are present in only 53% of patients with alcoholic WE, but carry a specificity of 93%. A systematic review of WE after bariatric surgery found that 47% of patients had normal brain CT and MRI studies. Our patient had no MRI abnormalities.

Parenteral administration of thiamine rapidly improves symptoms by producing a steep concentration gradient between plasma and brain, allowing for rapid passive diffusion. This route is preferred because even in ideal circumstances, only 4.5 mg of thiamine can be absorbed from a single oral dose, given rate-limited absorption. In patients with WE following bariatric surgery, underlying malabsorption issues make parenteral administration even more advisable. A 2013 Cochrane review found that no good evidence is available from randomized control trials to guide thiamine dosing in WE. However, an accepted treatment regimen is 500 mg thiamine given intravenously 3 times a day for 3 days, followed by 250 mg thiamine given intravenously or intramuscularly once a day for 5 days.

The efficacy of treatment with thiamine in WE depends on disease severity at presentation and time elapsed before treatment. In one systematic review of WE after bariatric surgery, most patients made a complete recovery.
another review, approximately half of the patients had lasting neurologic dysfunction, and only 2 of 16 patients who presented with advanced bariatric WE had a complete recovery. Patients have also died from bariatric-associated WE.49 This case report has several limitations. The patient was not an ideal historian and was initially not forthcoming about her vitamin nonadherence. Furthermore, the medical records leading up to her presentation were incomplete. Thus, it is challenging to assess the severity of her symptoms and degree of improvement after treatment. Unfortunately, we have not been able to reach the patient by phone since her discharge, so it is unknown if she has experienced long-term neurologic dysfunction.

In summary, a 34-year-old woman who presented with bilateral leg weakness and diplopia 11 months after Roux-en-Y gastric bypass surgery was found to have bariatric-associated WE due in part to vitamin nonadherence stemming from the high cost of vitamin supplementation. She experienced a partial recovery following treatment with parenteral thiamine. To our knowledge, this is the first reported case of bariatric WE in which the high cost of nutritional supplementation contributed to medication nonadherence. Because there is a lifelong need for vitamin supplementation following bariatric surgery, and because such supplementation is typically not covered by insurance companies, it is imperative that patients understand the importance of and costs associated with vitamin supplementation before they undergo surgery. Furthermore, providers must maintain a high level of suspicion for vitamin nonadherence in post-bariatric surgery patients. And additionally, they should always consider WE in their differential diagnoses when these patients present with symptoms like weakness and oculomotor abnormalities.

**Conclusion**

We stress the importance of recognizing the causes of medication nonadherence in the setting of bariatric surgery and the early neuro-ophthalmic manifestations of Wernicke encephalopathy in order to prevent devastating neurologic deficits and even death. In our own practice, we will routinely follow up with postbariatric patients to discuss vitamin adherence and maintain a low threshold for treating such patients empirically with IV thiamine whenever WE is on our differential. Continued opportunities for research exist for understanding the differences between alcoholic and bariatric-associated WE, predicting which bariatric patients will develop WE, and diagnosing and treating thiamine deficiency before it progresses to WE. On a policy level, insurance companies should consider covering postbariatric vitamin regimens to help eliminate cost as a barrier to vitamin adherence.

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