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A BERIBERI UNHEALTHY LATTE: ENCEPHALOPATHY AND SHOCK FROM SEVERE NUTRITIONAL DEFICIENCY

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□ **Abstract—Background: Thiamine deficiency is an uncommon cause of severe illness in the United States that can lead to significant morbidity because of high-output cardiac failure, peripheral neuropathy, and permanent neurologic impairment. We report the case of a middle-aged woman with extreme malnutrition caused by complications of Roux-en-Y gastric bypass (RYGB) surgery who presented with signs and symptoms of severe thiamine deficiency and septic shock. Case Report: A 43-year-old woman who had undergone RYGB surgery and who had multiple complications presented to the emergency department with agitation, confusion, and lethargy. The physical examination revealed an obtunded woman appearing much older than her reported age with significant peripheral edema. She was hypoxemic, hypotensive, and febrile. The initial laboratory analysis revealed a serum lactate level above the measurable limit, a normal thyroid-stimulating hormone, and elevated levels of troponin and brain natriuretic peptide. A transthoracic echocardiogram showed high-output heart failure. The patient's family later revealed that for the past year her diet had consisted almost exclusively of frozen blended lattes. High doses of thiamine and folate were started. Her shock, hyperlactatemia, and respiratory failure resolved by hospital day 3 and her encephalopathy resolved soon thereafter. Why Should an Emergency Physician be Aware of This?: Thiamine deficiency is a rare but reversible cause of shock, heart failure, and encephalopathy. Identifying patients who are at risk for severe nutritional deficiencies may aid in more rapid treatment with relatively benign medications with little downside, in this case high-dose vitamin B_1, and ultimately improve patient-oriented outcomes such as mortality, morbidity, and hospital length of stay.**

□ **Keywords—Beriberi; High-output heart failure; Lactate; Nutritional deficiency; Sepsis; Wernicke encephalopathy**

INTRODUCTION

Thiamine deficiency is an uncommon cause of severe illness in the United States. It is most prevalent in the alcoholic population as well as patients with malabsorption syndromes, particularly after gastric bypass surgery (1). The published literature shows that ≤49% of patients post–Roux-en-Y gastric bypass (RYGB), a commonly performed bariatric surgery, may be thiamine deficient by serum testing (1). Failure to consider this diagnosis in acute presentations of altered level of consciousness in patients post–bariatric surgery and those who are alcoholics can lead to significant morbidity caused by multisystem organ failure, including high-output cardiac failure (wet beriberi), peripheral neuropathy, and permanent neurologic impairment from Wernicke–Korsakoff syndrome

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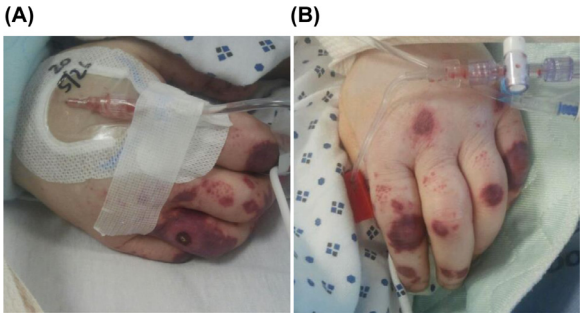

Figure 1. Skin lesions on admission . Note the striking edema. (A) Right hand. (B) Left hand.

(2). The severe malnutrition underlying this disorder may also lead to an immunosuppressed state that predisposes patients to infection with atypical organisms. We submit the case of a middle-aged woman with extreme malnutrition secondary to complications of RYGB surgery who presented with signs and symptoms of severe thiamine deficiency, as well as septic shock from group G streptococcus.

CASE REPORT

A 43-year-old woman with a medical history notable for RYGB complicated by multiple revisions including splenectomy and the development of intestinal malabsorption with resultant bowel incontinence, chronic pain, asthma, and posttraumatic stress disorder was brought to the emergency department by her family after the acute development of agitation, confusion, and lethargy. This acute change was preceded by several days of progressive violaceous red lesions on her hands and bilateral lower extremities (Figure 1). The patient had also developed significant lower extremity edema, shortness of breath, and difficulty walking, with an unsteady gait.

The physical examination revealed an obtunded woman appearing much older than her reported age with significant peripheral pitting edema. Her initial vital signs were remarkable for a heart rate of 112 beats/min, a temperature of 38.5°C, a respiratory rate of 29 breaths/min, blood pressure of 74/36 mm Hg, and an oxygen saturation of 86% on room air. The patient was nonresponsive to voice but intermittently moved all extremities. Her pupils were medium sized, equal, and reactive and without rotary or vertical nystagmus. She was tachycardic without any murmurs or gallops. The patient was tachypneic with moderate accessory muscle use and paradoxical abdominal movements. Bibasilar crackles were noted on auscultation. Her abdomen revealed multiple surgical scars but no obvious tenderness to palpation. Bowel sounds were present. Multiple nonblanching violaceous lesions on her hands and feet were identified (Figure 1). Small cracks were noted on her toes and heels with surrounding erythema.

Immediate resuscitative efforts were initiated and she was intubated for airway protection. Intravenous (IV) piperacillin-tazobactam and vancomycin were administered and, after aggressive fluid resuscitation, norepinephrine, and then vasopressin were started for persistent hypotension and shock. She had profound hypoxemic respiratory failure requiring high levels of inspired oxygen (100%) and positive-end expiratory pressure. Her initial chest radiograph is shown in Figure 2.

The initial laboratory analysis was remarkable for a serum lactate that was above the measurable limit (>11 mg/dL), a normal thyroid-stimulating hormone (2.56 mIU/mL; normal 0.27–4.20 mIU/mL), microcytic anemia (hemoglobin 8.5 g/dL [normal 11.2–15.7 gm/dL] and mean corpuscular volume 72.4 μm^3 [normal 79.0–95.0 μm^3]), an elevated troponin T level (0.13 ng/mL; normal <0.01 ng/mL), and an elevated brain natriuretic peptide level (532 pg/mL; normal <100 pg/mL). Blood, urine, and sputum cultures were obtained and she was transferred to the intensive care unit for further management. Her hyperlactatemia persisted despite aggressive resuscitation and improvement in her hemodynamics. A transthoracic echocardiogram was obtained shortly after admission and showed normal left ventricle/right ventricle systolic function with an elevated left ventricular ejection fraction of 77%, elevated right atrial pressure (15–20 mm Hg), and a right ventricular systolic pressure of 50 mm Hg, suggestive of pulmonary hypertension and high-output heart failure.

Further history was obtained from the patient's family, who revealed that for the past year her diet had consisted almost exclusively of a popular franchise's blended iced coffee drink. High doses of thiamine and folate were started at this time. While there is a paucity of high-quality evidence regarding thiamine dosing for acute beriberi, the patient was started on an often-cited regimen of 500 mg IV 3 times daily for 3 days followed by 250 mg IV daily and continued until clinical improvement ceased (3). She was then continued on 100 mg of oral thiamine daily indefinitely. Folate supplementation of 1 mg IV daily was continued throughout her hospitalization. Blood cultures subsequently grew group G streptococcus and antibiotic coverage was narrowed to penicillin G. Her shock and respiratory failure resolved by hospital day 3 and she received aggressive diuresis with a marked decrease in her peripheral edema and resolution of her pulmonary edema. Her lactate levels normalized around this time.

Case Resolution

The patient remained comatose despite 2 days without sedation. A lumbar puncture and continuous electroencephalogram were performed and unremarkable. After

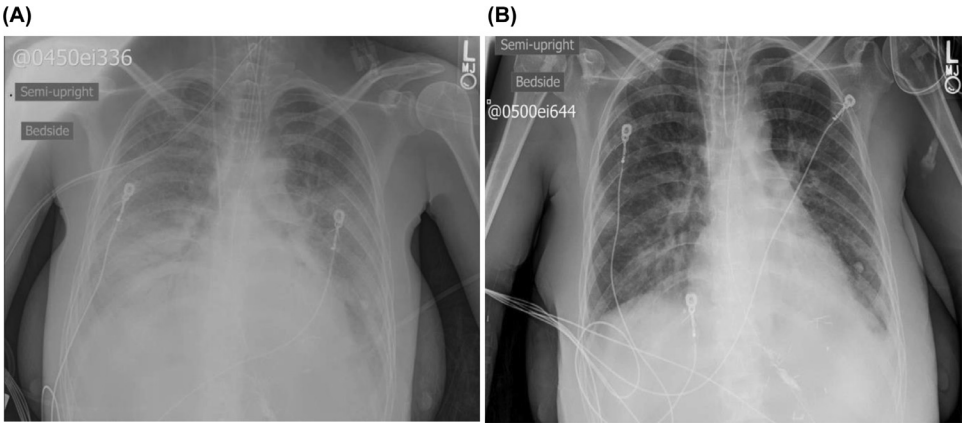

Figure 2. Improvement in chest radiograph after aggressive management. (A) Initial anterior-posterior portable chest radiograph showing marked pulmonary edema. (B) Anterior-posterior portable chest radiograph on hospital day 4.

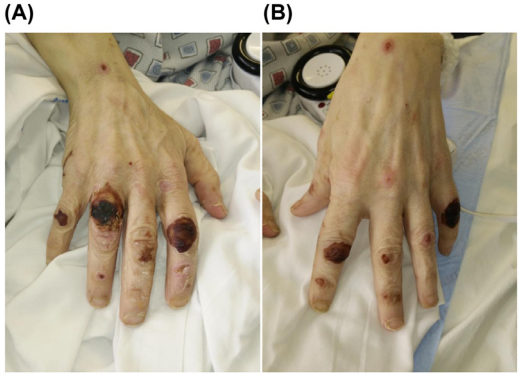

Figure 3. Skin lesions at time of discharge. (A) Right hand. (B) Left hand.

approximately 3 days without sedation, she awoke spontaneously and was extubated without complication. The patient improved rapidly with the resolution of her encephalopathy and was transferred out of the intensive care unit on hospital day 8. She remained hospitalized for an additional week as she remained mildly febrile. Her skin lesions improved significantly during her stay and she was discharged to a skilled nursing facility 16 days after admission (Figure 3). It was postulated by infectious disease specialists that the portal of entry for the group G streptococcus was from the patient's dog licking cracks on the patient's feet.

DISCUSSION

We submit a complicated case of a patient with a history of RYGB surgery and splenectomy who presented to our emergency department in shock from group G streptococcus septicemia and high-output heart failure secondary to thiamine deficiency from a diet primarily consisting of a frozen caffeinated beverage that contains no thiamine. This case is of particular significance to the emergency physician because of the importance of recognizing nutritional deficiencies as a potentially reversible cause of critical illness. Her complex presentation with a seemingly unrelated constellation of long-standing lower extremity peripheral neuropathy resulting in ataxia, high-output cardiac failure, encephalopathy, and memory impairment are classic for this easily overlooked vitamin deficiency. Her profoundly elevated lactate with impaired clearance despite an improvement in hemodynamics was another clue hinting at the diagnosis.

Thiamine Deficiency

Thiamine is an essential vitamin required for oxidative metabolism. It is primarily absorbed in the duodenum and crosses the blood–brain barrier (3). Humans have a limited storage capacity for thiamine with the liver being the main extramuscular storage site. Symptoms of thiamine deficiency can develop after only a few weeks of a thiamine-restricted diet (3,4). Patients with RYGB anatomy are at particularly high risk of thiamine and other nutritional deficiencies because of their altered enteric absorption. Given thiamine's crucial role in oxidative metabolism, deficiency primarily affects the nervous and cardiovascular systems because of their high energy requirements (5). The resulting clinical syndromes are classically divided into wet beriberi, characterized by high-output heart failure, and dry beriberi, characterized by peripheral polyneuropathy, ataxia, and encephalopathy. A mixed presentation may occur and is generally termed thiamine deficiency with cardiopathy and peripheral neuropathy (6,7). Thiamine pyrophosphate, the vitamin's active form, is also a key coenzyme in the metabolism of lactate to pyruvate and thus thiamine deficiency can result in profound hyperlactatemia, as shown in this case (8).

Neurologic Manifestations of Thiamine Deficiency

Thiamine has several important functions in the nervous system, including myelin sheath maintenance, neurotransmitter synthesis, and synaptic axonal transmission (9,10). Accordingly, thiamine deficiency results in sensory and motor neuropathies that primarily affect the distal extremities, often leading to ataxia. Wernicke encephalopathy (WE), a severe form of dry beriberi, is the most common manifestation of thiamine deficiency in developed countries. The classic triad of WE (oculomotor abnormalities, cerebellar dysfunction, and altered mental status) is seen in only a minority of patients with severe thiamine deficiency (3). As a result, Caine et al. developed a series of criteria to better identify patients with this syndrome (11). A positive diagnosis is achieved when 2 of the 4 following criteria are met: 1) dietary deficiency; 2) oculomotor abnormalities; 3) cerebellar dysfunction; and 4) either altered level of consciousness or mild memory impairment (11). These criteria are significant because failure to recognize this syndrome may lead to permanent neurologic deficits in 75% of patients and carries a mortality rate as high as 20% (12). While there are multiple laboratory and imaging studies that can aid in the diagnosis of WE, it remains a clinical diagnosis. Importantly, serum thiamine levels do not always correlate with brain thiamine levels and a normal serum thiamine level does not exclude WE (13). Typical treatment involves supplementing the patient with high-dose IV thiamine, up to 1500 mg daily (3). The response to thiamine therapy is variable. Ophthalmoplegia typically resolves within hours and ataxia within days, while encephalopathy and cognitive deficits may persist for weeks, as was the case with our patient. Some deficits in short-term memory and coordination may be either long-term or permanent (3).

Cardiovascular Manifestations of Thiamine Deficiency

Within the cardiovascular system, thiamine deficiency may cause direct vasomotor depression by severely limiting oxidative metabolism, leading to decreased systemic vascular resistance, increased blood volume, and increased cardiac output. This high-output state is followed by myocardial depression and ultimately decreased cardiac output (14,15). The most common constellation of signs and symptoms in patients with wet beriberi include dyspnea, orthopnea, pulmonary and peripheral edema, warm extremities, an elevated cardiac output, and elevated mixed venous oxygen content (3,16). Although this is less commonly observed than dry beriberi, it is equally if not more important because patients may present with encephalopathy caused by hypoxemia or end organ ischemia as well as symptoms of shock and may require immediate resuscitative efforts (17).

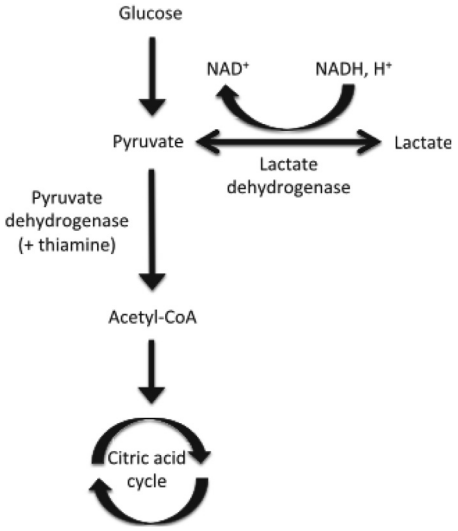

Figure 4. Biochemical pathway of glucose metabolism showing the role of thiamine and production of lactate. CoA = coenzyme A; NAD = nicotinamide adenine dinucleotide; NADH = nicotinamide adenine dinucleotide plus hydrogen.

Bariatric Surgery, Lactate, and Thiamine Deficiency

As shown in Figure 4, thiamine is an essential cofactor for the conversion of pyruvate to acetyl coenzyme A and entry into the Kreb's cycle. A lack of thiamine will lead to elevated lactate levels because of the conversion of accumulated pyruvate to lactate (18). A review of the literature reveals a multitude of reports of peripheral neuropathies in patients after various forms of bariatric surgery (1,19–21). In 1 large retrospective study of 457 patients undergoing gastric bypass surgery, Abarbanel et al. reported that 52% of patients suffered peripheral neuropathy up to 20 months after surgery (22). In addition, up to one-third of all bariatric surgery patients suffered persistent emesis, which likely predisposes them to further nutritional deficiencies (22). Other studies have shown the development of new onset myelopathies and polyneuropathies $\leq$18 years after surgery. Urinary incontinence has also been observed in this population (20).

Malnutrition and Sepsis

Patients at risk for thiamine deficiency are almost uniformly severely malnourished, leading to an immunocompromised state and placing them at higher risk for sepsis from both typical and atypical organisms. Thiamine deficiency does not appear to directly lead to immunosuppression or contribute to sepsis, although the published

literature in this area is limited. The early initiation of broad-spectrum antibiotics is essential in the critically ill patient with suspected sepsis because this has been shown to improve mortality (23). Furthermore, while recent randomized controlled trials suggest there is no role for routine vitamin therapy in sepsis and septic shock, this case serves as a reminder that patients with severe underlying malnutrition who may be at risk for vitamin deficiencies might benefit from targeted supplementation (24).

Splenectomy and Sepsis

Our patient had also undergone a splenectomy, which negates the spleen's critical opsonization, filtration, and anti-inflammatory functions. Asplenic patients have less effective and delayed immunoglobulin production, diminished phagocytic function in the absence of splenic macrophages, and diminished filtration because of the loss of splenic architecture (25). These deleterious immunologic changes greatly increase patients' susceptibility to infection, especially because of polysaccharide-encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae* type B, *Neisseria meningitidis, Escherichia coli*, Salmonella species, *Klebsiella pneumonia*, group B streptococci, and *Pseudomonas aeruginosa* (25). Asplenic patients are also at higher risk for severe infection. Overwhelming postsplenectomy infection is a subset of postsplenectomy infections that results in fulminant sepsis and carries a particularly high mortality rate (≤50%–70%) (26). One proposed cause of overwhelming postsplenectomy infection is loss of the spleen's critical role in attenuating the proinflammatory cytokine cascade in sepsis (25,27). Vagal stimulation is thought to attenuate splenic macrophage tumor necrosis factor production and instead promote anti-inflammatory cytokine release (27). Losing this splenic anti-inflammatory pathway may make asplenic patients more likely to develop an overwhelming and dysregulated inflammatory cascade (27). While it is not clear to what extent our patient's course was influenced by her asplenia, she was certainly at high risk for fulminant sepsis.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Thiamine deficiency is a rare but readily reversible cause of shock, heart failure, and encephalopathy, 3 commonly encountered presentations of critical illness. While most emergency physicians readily associate alcoholism with thiamine deficiency, it is important to consider thiamine deficiency as a contributing factor to critical illness in other populations, particularly in patients who have undergone bariatric surgery, an increasingly common procedure. Ophthalmoplegia may resolve rapidly after high-dose thiamine while encephalopathy may persist for weeks. Although recent well-publicized clinical trials have shown no benefit from empiric vitamin therapy in septic shock, vitamin supplementation may be beneficial in select patients. Identifying patients who are at risk for severe nutritional deficiencies may aid in more rapid treatment with relatively benign medications with little downside, in this case high-dose vitamin B_1, and ultimately improve patient-oriented outcomes such as mortality, morbidity, and hospital length of stay.

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