Clinical Vignettes

Elevated Lactate Secondary to Gastrointestinal Beriberi

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Thiamine deficiency usually occurs with prolonged nutritional deficiency and is almost universally identified with Wernicke's encephalopathy or beriberi. It is also, however, a rare cause of elevated lactate and gastroenterological symptoms. This case report describes a 30-year-old man with 2 weeks of gastroenterological symptoms and intermittent oral intake, who was found to have an elevated lactate level. Neurological exam was normal and an extensive workup was negative, but after being treated with thiamine, his lactate level improved overnight and all of his symptoms resolved. Thiamine levels returned low at 44 nmol/L (normal 78–185 nmol/L). Lack of recognition of this phenomenon, while rare, can lead to unnecessary tests and procedures and increased morbidity and mortality.

KEY WORDS: Phrases to use in indexing; Thiamine deficiency; Thiamine malabsorption; Elevated lactate; Gastrointestinal beriberi; Morbidity.

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INTRODUCTION

Thiamine deficiency most commonly manifests as beriberi or Wernicke's encephalopathy, and is an easily overlooked cause of gastrointestinal symptoms and lactic acidosis in severely ill patients.^{1,2} The following report reviews the case of a patient without common risk factors for thiamine deficiency who developed an elevated serum lactate level that resolved rapidly following thiamine infusion.

CASE

A 30-year-old man with past medical history significant for 4 years of intermittent abdominal pain of unknown etiology presented with sharp, right-upper-quadrant pain of 2 weeks duration associated with nausea and non-bloody vomiting of 1 week duration. He denied sick contacts, recent travel, or any past or current alcohol use. He reported eating a normal diet. He took no prescribed, over-the-counter, or herbal medications, but did endorse 12 years of daily marijuana use.

Upon presentation, his vital signs revealed a heart rate of 117 beats/min, blood pressure of 155/106 mmHg, temperature of 37.1 °C, and oxygen saturation of 100 % breathing room air. Physical examination was notable for a well-nourished 30-year-old man in moderate distress. Cardiopulmonary examinations were normal. His abdomen was soft and non-distended, but diffusely tender with deep palpation. Murphy's sign was positive and Rovsing's sign was negative. He did not have hepatosplenomegaly, and bowel sounds were normoactive. Musculoskeletal and neurological exams were entirely normal.

Initial workup revealed a leukocytosis of 21,000 cells/mcL without bandemia, an anion gap of 21 mEq/L with an elevated serum lactate level of 2.6 mEq/L (normal 2.2 mEq/L), and a mildly elevated aspartate aminotransferase (AST) of 48 IU/L (normal 0–40 IU/uL). All other serum chemistry, renal function tests, liver function enzymes, and lipase were within normal limits. A venous blood gas performed in the emergency department showed a pH of 7.44, pCO₂ of 32 mmHg, oxygen saturation of 89 %, and a bicarbonate level of 22 mmol/L. A hepatobiliary iminodiacetic acid (HIDA) scan was performed, given his positive Murphy's sign, and was negative. An abdominal CT scan showed thickening of the distal wall of the stomach, possibly due to peptic ulcer disease. For this reason, he was given an initial diagnosis of peptic ulcer disease with suspected gastritis versus gastroenteritis. He was initiated on treatment with a pantoprazole drip, bowel rest, intravenous (IV) fluids, ondansetron, promethazine, and ciprofloxacin and metronidazole to cover for gram-negative and anaerobic gastrointestinal bacterial infections.

He tolerated a regular diet on day 3, but his symptoms of nausea, vomiting and abdominal pain recurred. A CT angiogram of the abdomen and pelvis was obtained on day 4, which did not show mesenteric ischemia or any other intra-abdominal abnormalities. An esophagogastroduodenoscopy was performed, and he was found to have chronic gastritis and a cratered, acute, benign-appearing duodenal ulcer. A biopsy of the ulcer did not show evidence of *Helicobacter pylori* infection. Meanwhile, the patient's liver function tests worsened to an AST of 134 and an alanine aminotransferase (ALT) of 187 IU/L by day 10. Serum lactate levels increased to 8.0 mEq/L with an anion gap of 23 by day 10. He continued to have a persistent leukocytosis to 18,000 cells/mcL without bandemia. Lipase, urine ketones, and blood chemistries including renal function tests remained normal. Rhabdomyolysis was considered, and creatine kinase level was found to be 672 IU/L,

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but the patient lacked risk factors and did not complain of any muscle pains or weakness. Blood and urine cultures obtained on admission and repeat cultures did not find any source of infection. Liver ultrasound was unremarkable. Repeat CT of the abdomen and pelvis did not show perforation or other abnormality. HIV, hepatitis panel, thyroid function, celiac disease, autoimmune hepatitis, anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), and arsenic and lead bloodwork testing all returned negative. Stool studies were likewise negative.

At this time, the patient's diagnosis was unclear. His symptoms were not improving with appropriate therapy for his duodenal ulcer and gastritis. We considered a diagnosis of cannabinoid hyperemesis based on his daily marijuana use, but we expected that he should have improved with cessation. It was day 11 when a new symptom developed. He reported tingling in his chest, below his sternum. Otherwise, a physical exam, including a thorough neurological exam, continued to remain unremarkable.

On day 11, based on a literature review of elevated serum lactate levels, we considered that he may have thiamine deficiency. Serum thiamine levels were drawn and a trial infusion of IV thiamine was given. The following day, with no other new interventions, the serum lactate levels decreased from 8.7 to 2.3 mEq/L and his nausea and vomiting stopped. The patient was discharged on hospital day 13 with all of his symptoms resolved. His thiamine level that had been drawn prior to treatment returned at 44 nmol/L (normal 78–185 nmol/L). A brief encounter with the patient 7 months later found him taking thiamine supplementation and doing well.

DISCUSSION

Thiamine deficiency as a cause of elevated lactate is described in the literature, but prior reports have typically included a prolonged period of nutritional depletion, being extremely ill (often requiring intensive care unit [ICU] level of care), or having neurological or cardiovascular changes.¹ This case was an unusual presentation of thiamine deficiency because the patient had none of those factors.

Thiamine (vitamin B1) is a water-soluble vitamin that is an essential component for cellular metabolism. Deficiency of thiamine can cause beriberi and Wernicke–Korsakoff syndrome. The thiamine cation is absorbed in the duodenum and converted to thiamine pyrophosphate (TPP). TPP is a required cofactor for pyruvate dehydrogenase and α -ketoglutarate dehydrogenase, which are essential components in the tricarboxylic acid cycle and aerobic carbohydrate metabolism, with α -ketoglutarate dehydrogenase being rate-limiting for the function of the tricarboxylic acid cycle.³ In thiamine deficiency, α -ketoglutarate dehydrogenase activity is substantially reduced, leading to decreased carboxylic acid

cycle flux, decreased entry of pyruvate into the cycle, and shunting of glucose carbon to lactate (Fig. 1).^{4,5} Thiamine deficiency is one of many possible causes of elevated lactate described by Anderson et al.⁶

The mechanisms for thiamine deficiency include inadequate diet, impaired storage and use by the liver, excessive requirements for thiamine induced by increased environmental temperature, or metabolism of alcohol or diets high in carbohydrates, and inborn enzymatic defects.⁷ Physicians should be aware of key risk factors including alcohol abuse, gastric bypass, systemic diseases such as AIDS and renal disease, and unbalanced nutrition (Table 1). Deficiency usually manifests as the classical clinical disorders of Wernicke encephalopathy or wet or dry beriberi.¹ However, an under-recognized gastrointestinal syndrome of thiamine deficiency consisting of nausea, vomiting, abdominal pain and lactic acidosis was first described in two patients by Donnino in 2004, and is known as gastrointestinal beriberi.²

The patient in this case showed characteristics of gastrointestinal beriberi including nausea, vomiting, and abdominal pain, the elevated lactate levels and anion gap, the rapid resolution of symptoms after thiamine administration, and the low blood thiamine levels.^{8,9} Additional findings not described as gastrointestinal syndrome but present in this case include leukocytosis, elevated transaminases, and tachycardia. Perhaps these findings will be confirmed in future cases of thiamine deficiency with gastrointestinal symptoms.

It remains unclear what caused the patient's thiamine deficiency. His vomiting alone fails to explain his deficiency. Even with 7 days of poor intake prior to admission and then 12 days of bowel rest, he would just be reaching the body's estimated 18-day reserve.¹⁰ The patient also reported weekly intake of pasta, which is a good source of the nutrient. The leading hypothesis to explain the deficiency in this case is as a complication of long-standing peptic ulcer disease. He was noted to have 4 years of intermittent abdominal pain, and was diagnosed with a duodenal ulcer while admitted. Peptic ulcer disease has been proposed as a rare cause of thiamine deficiency due to malabsorption.¹¹ While treatment with thiamine clearly resolved the patient's signs and symptoms, it is less clear when the thiamine deficiency started to cause dysfunction. At least two scenarios are plausible. One, the patient's ulcer, possible cannabinoid hyperemesis, or another cause resulted in abdominal pain, vomiting, and poor food intake, and that along with bowel rest led to thiamine deficiency. Or two, most of the patient's findings prior to and during admission were due to thiamine deficiency. The deficiency may have been caused by long-standing malabsorption or another cause. Of note, the patient's peripheral venous blood gas on admission showed higher than expected room air oxygen saturation of 89 %. This is consistent with central venous hyperoxia seen in the reported cases of gastrointestinal

Fig. 1 Thiamine’s role in the glycolytic and TCA cycle pathways. *α-KDH* α-ketoglutarate dehydrogenase, *PDH* pyruvate dehydrogenase, *TCA* tricarboxylic Acid, *TPP* thiamine pyrophosphate

beriberi, where mitochondrial defect in oxygen utilization is caused by thiamine deficiency.²

Insufficient thiamine as a cause of elevated lactate is easily and inexpensively treated, and should be considered in cases of unexplained elevated lactate levels, especially those who

concurrently present with gastrointestinal symptoms not otherwise explained.⁶ The described patient was difficult to diagnose due to a lack of risk factors for thiamine deficiency, the concurrent presence of a duodenal ulcer, and a lack of neurological findings besides chest tingling.¹²

Outcomes of delayed diagnosis of thiamine deficiency as a cause of elevated lactate and gastroenterological symptoms can lead to unnecessary tests, procedures, and even death.^{13,14} In this case, an initial lack of consideration of thiamine deficiency led to the patient having an unnecessary repeat abdominal CT scan and CT angiography, and ultimately a prolonged hospital stay. While thiamine deficiency is now commonly associated with alcohol abuse, suspicion should be maintained for gastrointestinal surgery and fad diets as causes, including in the obese. Detailed surgical and dietary histories can be critical in making the correct diagnosis. When faced with elevated lactate levels in patients with and without sepsis, it is important to consider a multifactorial etiology, such as thiamine deficiency and liver dysfunction. A systematic approach to elevated lactate is essential. Failure to properly diagnose and treat similar cases will result in wasted health care expenditures, morbidity and mortality.

Table 1 Risk Factors for Thiamine Deficiency
Risk factors for thiamine deficiency ^{10,15–17}
Alcohol misuse and malnutrition
Unbalanced nutrition including absolute food deficiency, voluntary fasting, neglect in old age, unbalanced total parenteral nutrition, use of dietary commercial formula, and chronic use of food containing thiaminases
Gastrointestinal surgical procedures such as gastric bypass and gastrectomy
Recurrent vomiting or chronic diarrhea, including vomiting due to peptic ulcer, anorexia nervosa, pancreatitis, or hyperemesis gravidarum
Systemic diseases including AIDS, renal diseases, and chronic infectious febrile diseases
Cancer and chemotherapeutic agents
Magnesium depletion
Use of chemical compounds, including intravenous infusion of nitroglycerin
Staple diet of polished rice (most prevalent in Asian countries)

Acknowledgments: Contributors: Carrie Duca, BA -Fig. 1.

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