Case in Point

Forgotten but Not Gone? A Probable Case of Wet Beriberi

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Thiamine deficiency may be more prevalent than is recognized. These authors describe a case of probable wet beriberi, outline challenges in making this diagnosis, review factors that may precipitate the disorder, and discuss treatment.

In the United States, malnutrition is a common and severe medical problem. The obesity epidemic is well recognized. But overconsumption of calories does not guarantee adequate nutrition. Many Americans are deficient in important micronutrients. Cordain and colleagues report that one-third of Americans are deficient in folate, as defined by the U.S. recommended dietary allowances from 1989, and 30% of Americans are deficient in thiamine by the same criteria.[1] Recognizing micronutrient deficiencies can be difficult. The authors present a case of thiamine deficiency, or beriberi, which was not clearly identified until its response to thiamine replacement.

Beriberi is a Sinhalese phrase that means "I cannot, I cannot," in reference to the profound weakness that may accompany the disorder. Beriberi is recognized as having 2 potential subtypes—a "wet" subtype, in which congestive heart failure is present, and a "dry" subtype, in which the peripheral or central nervous system is primarily symptomatic. The origin of beriberi dates back to ancient times, and until recently it was well recognized. At the end of the 19th century in Japan, for instance, the prevalence of beriberi among Japanese naval personnel was 50% of those at sea.[2]

The beginning of the end for beriberi as a disease without a cure was in the 1890s, when Christiaan Eijkman discovered that polished rice—but not rice with remnant of the hull still attached—caused the disease in chickens. This precipitated a search for the antineuritic factor contained in the hulls, resulting in the discovery of the first "vital amine," or vitamin: thiamine.[3] In the West today, vitamin deficiencies such as beriberi are often considered uncommon. This may result in underrecognition of potentially treatable cases.

O'Keefe and colleagues found that among 36 geriatric patients without dementia 31% had marginal evidence of thiamine deficiency, and another 17% had frank thiamine deficiency.[4] In a study of 50 terminally ill patients on a palliative care unit, borderline thiamine deficiency was found in 36% of patients and frank deficiency in another 28%.[5] The elderly, the very ill, and alcohol-dependent patients are among those at high risk for nutritional deficiencies; 30% to 80% of alcoholics may have some degree of thiamine deficiency.[6]

Given the prevalence of thiamine deficiency, it may seem odd that wet beriberi is not seen more often. This may be due to failure to recognize factors that may contribute to a thiamine deficiency, the frequent presence of stressors that may unmask a thiamine deficiency yet be mistaken as the etiology of the subsequent findings, and the symptoms of beriberi. The following case illustrates some of the factors that may both confound and clarify the presence of wet beriberi.

CASE REPORT

A 50-year-old Hispanic man with type 2 diabetes mellitus, diabetic neuropathy, hypertension, alcohol dependence, and tobacco abuse presented with a 25-pound weight gain over 2.5 months, abdominal distention, and lower extremity edema. On physical examination, his lungs were clear, he had a regular cardiac rate and rhythm with no murmurs, rubs, gallops, or third heart sounds. His abdomen was distended and 1+ peripheral as well as sacral edema was noted. He was tested for alcoholic cirrhosis and edema of unknown origin, and discharged on furosemide 40 mg twice a day and spironolactone 25 mg daily.

Three weeks later, the patient returned with worsening edema and abdominal distention, and new-on-

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set dyspnea at rest. He was taking his medications but was still drinking alcohol. His blood alcohol level was 266 mg/dL upon admission. His blood pressure was 117/78 mm Hg, respirations were 20 breaths per minute, and pulse was 110 beats per minute. Jugular venous distention (JVD) of 9 cm and 2+ peripheral edema ascending from his legs to his sacrum were noted. Rales were heard at both lung bases, as was a third heart sound and a 4/6 systolic ejection murmur. His cognition and cerebellar examinations were normal.

Laboratory tests revealed mild macrocytic anemia with mean corpuscular volume of 104.7 and folate deficiency. Thiamine replacement was initiated emergently, and before the thiamine level could be obtained. Aspartate aminotransferase and alanine aminotransferase were 62 IU/L (normal range: 13 IU/L to 47 IU/L) and 18 IU/L (normal range: 5 IU/L to 40 IU/L), respectively. Serum albumin was 2.6 g/dL (normal range: 3.0 g/dL to 4.6 g/dL). An abdominal computed tomography (CT) scan revealed mild cirrhosis with no other significant hepatic findings. Hepatitis panel was negative, alpha fetoprotein was within normal limits, and a triple-phase liver scan was unremarkable. Brain natriuretic peptide was within normal limits. An electrocardiogram (ECG) was unremarkable. A chest x-ray was remarkable only for a "small pleural effusion," which resolved during the patient's admission.

The patient was given furosemide 40 mg intravenously twice daily and spironolactone 50 mg intravenously daily with no improvement of peripheral edema or weight loss. The systolic ejection murmur and third heart sound were still audible, and bilateral rales were still present. The patient's peripheral neuropathy was unchanged. His cerebellar and cognitive examinations were normal. On hospital day 3, a trial of thiamine 200 mg orally daily was begun. Results were evident within the first 24 hours.

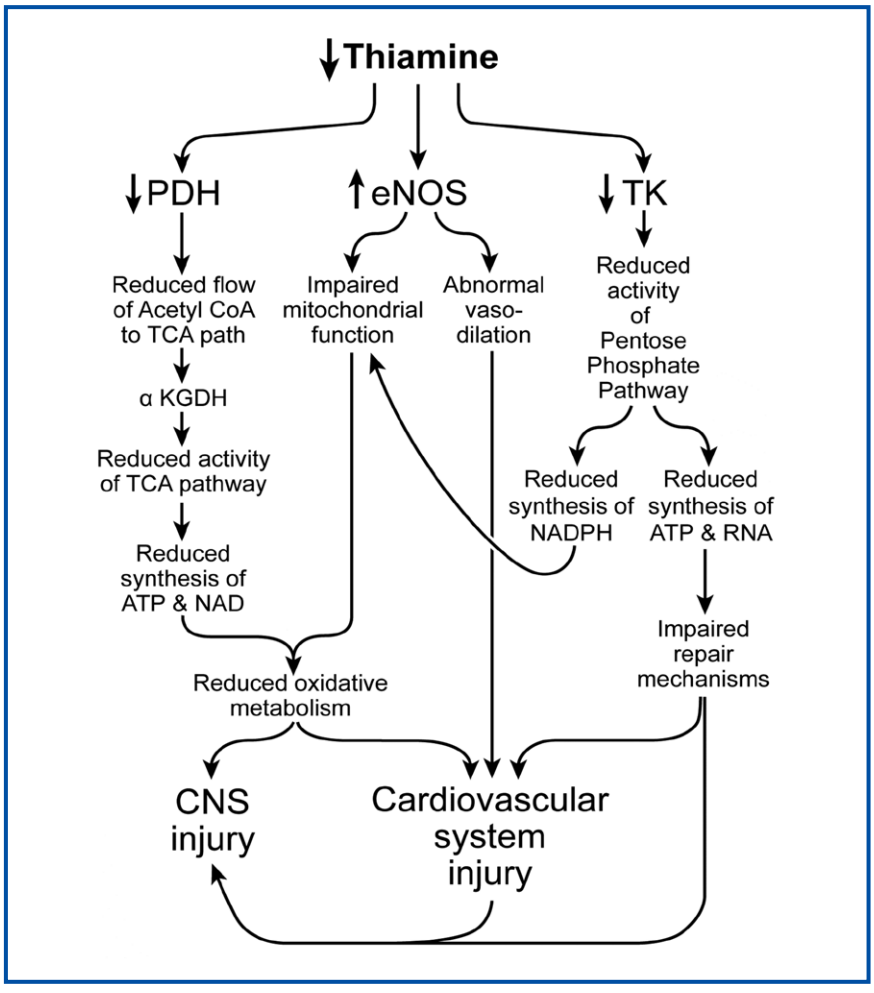

Figure 1. Key steps in the induction of beriberi. ATP = adenosine triphosphate; CNS = central nervous system; CoA = coenzyme A; eNOS = endothelial nitric oxide synthase; KGDH = alpha-ketoglutarate dehydrogenase; NAD = nicotinamide adenine dinucleotide; NADPH = nicotinamide adenine dinucleotide phosphate; PDH = pyruvate dehydrogenase; TCA = tricarboxylic acid cycle; TK = transketolase.

The patient dropped from 186.2 pounds to 176.3 pounds, and his peripheral edema improved. His JVD was improved at 7 cm and the systolic ejection murmur reduced to 2/6; the third heart sound was no longer audible. The patient noted a marked improvement in his sleep. Within 48 hours of beginning oral thiamine, JVD was 5 cm, and the peripheral edema and abdominal distention were much improved. The patient's dyspnea resolved, and the bilateral rales were diminished. He was discharged to home, and lost to follow-up. Although follow-up was arranged, the patient chose to not keep his appointments.

DISCUSSION

Pathophysiology

Thiamine deficiency may present in several ways. Classic presentations include Wernicke's encephalopa-

thy, dry beriberi—in which the peripheral nervous system is primarily affected—wet beriberi, Shoshin beriberi, and infantile beriberi (wet beriberi in an infant, which is otherwise indistinguishable in etiology and appearance from wet beriberi).[7,8] Thiamine is required by several enzymes involved in the production or metabolism of energy substrates, including pyruvate dehydrogenase (PDH), alpha-ketoglutarate dehydrogenase (AKGD), and transketolase (TK).[9] PDH and AKGD are components of the tricarboxylic acid cycle, a fundamental component of aerobic metabolism. TK is necessary for glycolysis and helps produce the high-energy compound nicotinamide adenine dinucleotide phosphate (NADPH).

Not surprisingly, rapid consumers of high-energy compounds, such as nervous and cardiac tissue, are particularly susceptible to impairments of the functions of these enzymes. Both neurons and astrocytes have high metabolic demands. Thiamine deficiency can impair the functioning of both, leading to abnormal release of neurotransmitters, such as glutamate, and reduced ability to maintain normal transmembrane ion gradients.[10] Thiamine stimulates the catalytic activity of PDH and additionally has a positive regulatory effect on PDH activity.[11] AKGD requires thiamine in the synthesis of nicotinamide adenine nucleotide (NAD), which, in turn, is critically important in aerobic metabolism. TK participates in the pentose phosphate pathway, another pathway with important roles in the synthesis of energy-storing compounds such as ATP and NADPH, as well as DNA and RNA.[12]

Similarly, cardiac myocytes are highly susceptible to impairments of oxidative metabolism, and in thiamine deficiency this impairment may translate into impaired contractile

Table 1. Diagnosing wet beriberi

Diagnostic factors	Significance
Exam findings	Lower extremity and sacral edema are classic, but while usually found, have low specificity[22] High-output heart failure and reduced peripheral resistance, as measured by diastolic blood pressure, and dyspnea are also classic
Laboratory findings	*Red cell transketolase*: the activity of this enzyme depends upon adequate thiamine levels[23] *Serum thiamine level*: serum levels of thiamine and its metabolites can identify deficiency states[24] *Serum lactate level*: lactic acidosis without shock can occur with thiamine deficiency[25] *Chest x-ray*: may reveal enlargement of the cardiac silhouette or pleural effusions, both reversible with treatment
Response to thiamine	Classically, a swift and robust response to thiamine typically appears within days. However, in some patients, response may be incomplete or even lacking

Table 2. Diagnosing dry beriberi

Diagnostic factors	Significance
Exam findings	*Peripheral polyneuropathy*: ascending, usually affecting legs more than arms initially, and face last; usually sensation affected more than motor function *Encephalopathy*: may be present, this being the classic Wernicke's type with impaired cognition, pancerebellar findings, and ophthalmoplegia, although all findings usually are not present
Laboratory findings	*Red cell transketolase*: the activity of this enzyme depends upon adequate thiamine levels[23] *Serum thiamine level*: serum levels of thiamine and its metabolites can identify deficiency states[24] *Serum lactate level*: lactic acidosis without shock can occur with thiamine deficiency[25]
Response to thiamine	Classically, a swift and robust response to thiamine appears, typically within days. However, in some patients response may be incomplete or even lacking

Table 3. Selected causes of thiamine deficiency

Causes	Pathophysiology
High-calorie carbohydrate diet	Increases demand for thiamine and can, over time, cause deficiency
Alcoholism	Alcohol is a source of calories but lacks thiamine. Often accompanied by reduced food intake
Loop diuretics	Markedly increase thiamine excretion[26]
Anorexia	Reduced oral intake of thiamine occurs in anorexia of all kinds, including chronic illness and psychiatric disease[27]
Hyperthyroidism	A hypermetabolic state increases demand for thiamine[28]
Parenteral nutrition	May contain inadequate thiamine, or be a marker for a hypermetabolic state[29]
Dialysis	Hemodialysis, and possibly other forms of dialysis, may remove thiamine or its metabolites from the circulation[30]
Diabetes	Over 70% of patients with type 1 and 2 diabetes have low serum thiamine levels due to increased renal thiamine losses[31]
Folate deficiency	Folate deficiency causes the intestinal thiamine transporter to take up folate, which can reduce thiamine uptake[32]
Coffee, tea, raw fish, shellfish	Thiaminases in these foodstuffs inactivate thiamine[9]

activity, and subsequent congestive heart failure.[13]

Another factor affecting both the brain and the heart is the effect of thiamine deficiency on endothelial function. In both the brain and the vasculature, enhanced inflammatory activity, including the increased synthesis and release of nitric oxide (NO) by endothelial nitric oxide synthase (eNOS), contributes to inflammatory injury and edema.[14] Within the heart, NO may affect both the timing of myocyte relaxation as well as the ability of myocytes to utilize oxygen.[15] Disturbances in NO synthesis and release may impair both of these functions. In the periphery, excessive release of NO by eNOS may promote dependent edema. In the brain, excess release of NO by eNOS appears to contribute to the selective damage typical of thiamine deficiency and Wernicke's encephalopathy. The activities of alpha-ketoglutarate dehydrogenase and of mitochondria, in general, are impaired by the excess release of NO from eNOS.[16]

In addition, congestive heart failure may selectively injure brain structures already sensitive to thiamine deficiency, such as the mammillary bodies and fornix.[17] It is unknown why, in some cases, thiamine deficiency tends to affect the cardiovascular system more than the nervous system, and vice versa. Figure 1 graphically depicts some of the key steps in the induction of beriberi.

Presentation and Diagnosis

Beriberi is classically divided into wet and dry forms. In wet beriberi, cardiovascular symptoms predominate. In dry beriberi, the nervous system is mainly affected. This distinction does seem to capture some clinical cases.[18] However, the clinician must be sensitive to 2 important facts: (1) The 2 forms of beriberi tend to travel together. (2) It is much more likely not to see a full, classic example of wet or dry beriberi than it is to see a few symptoms, which if untreated, may progress to an unmistakable picture of thiamine deficiency.

The initial difficulties in recognizing beriberi were well described by Igata. Between 1973 and 1975, Igata identified 73 cases of beriberi in a small area of Japan.[19] Detective work was required by Igata to determine that he indeed was seeing thiamine deficiency. Pretibial edema was almost always the sentinel complaint and was identified in all patients. Abnormal, deep tendon reflexes were observed in 72 of the 73 patients. Weakness was noted in 80%, sensory disturbances in just over 60%, and heart dilatation in about 50%. Reassuringly, Igata reported that "all

Table 4. Factors that may precipitate or aggravate wet beriberi	
Factors	**Pathophysiology**
Infection	May increase metabolic activity and thus demand for thiamine
Surgery	May increase demand for thiamine through increased metabolic activity, as well as reduce intake of thiamine in cases of bowel rest
Pregnancy	Increased metabolic activity may be accompanied by anorexia, nausea, and vomiting
Diarrheal illness	Can markedly reduce oral thiamine bioavailability
Liver disease	Reduced albumin synthesis may independently produce or aggravate edema
Alcoholic cardiomyopathy	An independent cause of heart failure
Glucose given before thiamine	Can stimulate metabolic pathways requiring thiamine and unmask a thiamine deficiency[33]

symptoms disappeared promptly by the administration of thiamine."[19] The presence of edema as the initial or only finding has previously been reported, and in prior case series "isolated involvement of the cardiovascular or nervous system was infrequent."[20] The challenge of recognizing mild or early beriberi is great.

The development of symptomatic thiamine deficiency is often gradual.[21] Wet beriberi is usually a high-output form of subacute or chronic cardiac failure. A fulminant form of wet beriberi also exists. This is called Shoshin beriberi and is characterized by acute hypotension, tachycardia, and lactic acidosis.[7] A thorough physical examination and medical history, as well as considering the possibility of malnutrition, are required to make the diagnosis of wet beriberi. Other causes of high-output cardiac failure, such as anemia and hyperthyroidism, should be considered, even though they do not exclude a diagnosis of wet beriberi. Table 1 lists some of the features and factors that help in making the diagnosis, and Table 2 lists features of dry beriberi; note the overlap.

As mentioned previously, the patient's medical history is an important factor in diagnosing wet beriberi. Eliciting a history of thiamine deficiency involves recognizing the many ways in which the uptake of thiamine may be blocked or its use abnormally increased. This is important of course, not just in helping to recognize the illness, but in treating it and establishing ways of preventing its recurrence. Table 3 is a brief outline of some of the causes of thiamine deficiency.

A simple way to conceptualize a patient at risk for thiamine deficiency is to think of someone who is potentially malnourished, as well as catabolic. Igata emphasized this interplay of diet and activity in his work, and railed against the carbohydrate-rich, thiamine deficient diet of the vigorous young men whom he saw as the face of thiamine deficiency. "Some young men, living alone," Igata wrote, "took 'instant noodle' at every meal, and then finally suffered from beriberi in a few months."[19] The medically ill patient with an inadequate diet faces a similar risk.

The role of catabolism in producing beriberi, if not recognized, may actually cause the clinician to miss the diagnosis. Because of its role in producing energy substrates, thiamine demand is sensitive to many types of physiologic stress. Before the role of thiamine in causing beriberi was recognized, it was assumed that an unknown bacillus must be involved, due in part to the association of beriberi with prior infections or other stressors. As noted by H. Wright in 1905, "Therefore, we not infrequently see beriberi after surgical operation, in chronic ulcer cases, and in parturient women."[21] For the modern clinician, who is less likely to encounter severe and untreated thiamine deficiency, the challenge has evolved to recognizing beriberi after a precipitating insult has been identified, rather than stopping at the diagnosis of the precipitating insult. Table 4 outlines factors that may precipitate or worsen wet beriberi.

Treatment

The treatment of any thiamine deficiency begins with thiamine replacement. As a water-soluble vitamin, thiamine is not stored in the body as well as fat-soluble vitamins. The body stores about 30 mg of thiamine. Roughly 0.5 mg of thiamine is needed for every 1,000 calories of food. Symptomatic deficiency can

develop in as little as 3 weeks of removing thiamine from the diet.[9] In the authors' institution, 100 mg daily of thiamine is the usual minimum replacement dose, and this may be given orally, intramuscularly, or intravenously. The idea is to flood the systemic circulation with thiamine to overcome factors that may limit its uptake or enhance its excretion, as well as the possibility of weak thiamine binding by the enzymes for which it is a cofactor.

At some point in the patient's care, a discussion about diet should occur. This discussion begins with a dietary history and, if necessary, ends with nutritional counseling. For high-risk patients, such as pregnant women, the chronically ill, or patients with a history of thiamine deficiency, ongoing thiamine supplementation can be helpful.

CONCLUSION

Wet beriberi is not yet a disease of the past. And in retrospect, this patient was a prime candidate for it: he was an alcoholic and diabetic with a low serum folate level who was taking furosemide for edema. He was at high risk for a low thiamine intake, reduced gut thiamine uptake, and iatrogenic enhancement of thiamine excretion. The patient's diagnosis of beriberi was based on his history and physical examination, and confirmed by his robust response to thiamine. The incomplete resolution of his symptoms may have been due to the brief period of thiamine treatment, ongoing use of furosemide, chronic liver disease, and possibly mild alcoholic cardiomyopathy. Given the substantial risk among some patient populations of thiamine deficiency, the safety of thiamine replacement, and the diagnostic value of a swift response to thiamine, the authors recommend that patients with severe edema or high-output cardiac failure be routinely considered for thiamine replacement.

Author disclosures

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