Thiamine deficiency: The importance of recognition and prompt management

In a recent *Nutrition* article, Bravata et al. [1] studied thiamine transporter genes in a patient with “sporadic beriberi.” This case illustrated how thiamine deficiency can present in clinical practice and why clinicians should be alert to its diagnosis and management.

Thiamine deficiency is no longer a clinical curiosity or limited to populations with suboptimal access to food [2]. Deficiency states occur often but may not always be recognized by the treating clinician as a result of a lack of familiarity with the condition, absence of “classic” signs and symptoms, and a lack of readily available confirmatory laboratory tests [3,4]. Clinical manifestations are myriad and may be confusing. It is puzzling as to why different patients present with various signs and symptoms. The study by Bravata et al. [1] dealing with the genetics of thiamine metabolism may provide us with answers.

Although thiamine deficiency often is associated with alcohol intake, consumption of a seemingly normal alcohol-free diet does not preclude its diagnosis. Thiamine deficiency is also common in obese patients and after bariatric surgery, patients with macronutrient excess but with micronutrient deficiency. Various medications (e.g., proton-pump inhibitors and metformin) are known to cause this deficiency. Thiamine deficiency may occur in critically ill patients, especially those on parenteral and enteral nutrition support.

Refeeding syndrome is another situation in which thiamine deficiency can rapidly occur. Cardiac failure with resultant dependent edema occurs in so-called “wet” beriberi, and neurologic manifestations are the hallmarks of “dry” beriberi. A diagnosis of delirium in the intensive care unit is rarely made without first considering Wernicke-Korsakoff syndrome. Other less known manifestations are “gastrointestinal beriberi,” presenting as severe abdominal pain; mimicking mesenteric vascular occlusion, and intestinal ischemia, with unexplained lactic acidosis. It is highly likely that different patients, or perhaps different subgroups or disease states, present with one or more of the varying manifestations of thiamine deficiency, depending on the gene or genes that are affected [5–17]. Some of the numerous causes of thiamine deficiency are depicted in Table 1.

The rapid resolution of edema in the case report [1] is surprising indicating an immediate effect of thiamine on cardiac function. Although this may be considered unusual for a vitamin in contrast to a medication, lactic acidosis and mental changes also can be rapidly reversed with parenterally administered thiamine. The daily oral requirement for thiamine is only about 1.2 mg. However, in clinical practice far greater doses of 100 to 300 mg/d are administered, also intravenously (although this can be associated with anaphylaxis in some patients and thus resuscitation precautions should be readily available). The high dose may override the metabolic blocks that may occur in patients with enzymatic defects caused by genetic mutation [2–4].

Thiamine deficiency is not uncommon. Some studies have reported a prevalence of the deficiency in about 10% to 20% of hospital patients. The human body cannot synthesize thiamine. Because humans usually only have stores of thiamine for about 2 wk, these can become depleted with poor intake. Thiamine stores can become depleted even earlier if other conditions are present (See Table 1). Broadly speaking, thiamine deficiency results from poor intake, reduced gastrointestinal absorption, renal loss, or increased metabolic requirements; many cases are multifactorial such as alcoholism and inadequate thiamine in parenteral nutrition [2–4].

Thiamine is principally absorbed in the jejunum and ileum, and, in the circulation, is mainly protein bound predominately to albumin. The vast majority of thiamine in the circulation is within erythrocytes. Thiamine has a specific binding protein called thiamine-binding protein (TBP). Thiamine and its metabolites are predominately renally excreted. Its cellular transport is mediated by specific thiamine-carrier transporters. Abnormalities of these genes may be associated with thiamine deficiency. Two main intestinal transporters of thiamine have been reported: the human thiamine transporter-1 (hTHTR-1), which is the product of *SLC19 A2* gene, and hTHTR-2, the product of *SLC19 A3*. Thiamine deficiency can induce intestinal carrier-mediated uptake by increased expression of hTHTR-2 [18–23].

One of thiamine’s active forms is thiamine pyrophosphate, which is an essential cofactor for various enzymes in carbohydrate metabolism such as pyruvate dehydrogenase, α-ketoglutarate dehydrogenase. Thiamine is involved in the decarboxylation of 2-oxoacids and the conversion of pyruvate to acetyl coenzyme A. Thiamine pyrophosphate is an essential cofactor for transketolase in the pentose–phosphate pathway. The latter enzyme is essential also for the integrity of the nervous system and repair of myelin nerve sheaths. Magnesium is an important cofactor for thiamine-dependent enzymes [2–4].

The *Nutrition* study [1] discussed genetic testing to look at thiamine transporter genes in a case of suspected and unexplained thiamine deficiency. Decreased plasma pyruvate and raised lactate concentrations may be clues as to the diagnosis of thiamine deficiency in the presence of a metabolic acidosis.
Table 1
Causes of thiamine deficiency

| Alcoholism          | Anorexia nervosa | Bariatric surgery | Chronic vomiting | Diabetes mellitus | Drugs (e.g., proton-pump inhibitors, metformin, high-dose diuretics) | Folate deficiency | Hemodialysis; chronic kidney disease | High dietary intake of thiaminases (e.g., betel nuts and raw fish) | HIV infection | Hyperemesis gravidarum | Intensive care and critically ill patients | Malabsorption states | Poor dietary intake especially if “excessive intake” of carbohydrate-rich foods | Refeeding syndrome | Spinocerebellar ataxia type 2 | Thiamine transporter-2 deficiency | Thiamine-responsive megaloblastic anemia syndrome | Thyrotoxicosis |
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[2–4]. Serum thiamine concentrations are not a reliable marker of the body’s thiamine status as they only represent a small proportion of total body thiamine.

The whole-blood or erythrocyte transketolase activity pre-loading and post-loading, with thiamine can be used to diagnose deficiency. An erythrocyte transketolase activation coefficient is usually >1.25 in biochemical thiamine deficiency. Erythrocyte thiamine diphosphate using high-performance liquid chromatography may now be a preferred assay to detect deficiency. It is also possible to measure urinary excretion of thiamine and its metabolites [2–4,24,25]. However, the diagnosis of thiamine deficiency is essentially a clinical one, as some of these assays are specialized and not always offered by routine hospital laboratories. Furthermore, these tests are potentially expensive, time-consuming, and not readily available [24,25].

In summary, clinicians should be vigilant for thiamine deficiency that can present in various clinical situations (Table 1). The diagnosis is mainly clinical and prompt thiamine replacement may reduce morbidity and mortality.

References