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Case report

Acute thiamine deficiency and refeeding syndrome: Similar findings but different pathogenesis

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ABSTRACT

Objective: Refeeding syndrome can occur in several contexts of relative malnutrition in which an overaggressive nutritional support is started. The consequences are life threatening with multi-organ impairment, and severe electrolyte imbalances. During refeeding, glucose-involved insulin secretion causes abrupt reverse of lipolysis and a switch from catabolism to anabolism. This creates a sudden cellular demand for electrolytes (phosphate, potassium, and magnesium) necessary for synthesis of adenosine triphosphate, glucose transport, and other synthesis reactions, resulting in decreased serum levels. Laboratory findings and multiorgan impairment similar to refeeding syndrome also are observed in acute thiamine deficiency. The aim of this study was to determine whether thiamine deficiency was responsible for the electrolyte imbalance caused by tubular electrolyte losses.
Methods: We describe two patients with leukemia who developed acute thiamine deficiency with an electrolyte pattern suggestive of refeeding syndrome, severe lactic acidosis, and evidence of proximal renal tubular dysfunction.
Results: A single thiamine administration led to rapid resolution of the tubular dysfunction and normalization of acidosis and electrolyte imbalance. This demonstrated that thiamine deficiency was responsible for the electrolyte imbalance, caused by tubular electrolyte losses.
Conclusions: Our study indicates that, despite sharing many laboratory similarities, refeeding syndrome and acute thiamine deficiency should be viewed as separate entities in which the electrolyte abnormalities reported in cases of refeeding syndrome with thiamine deficiency and refractory lactic acidosis may be due to renal tubular losses instead of a shifting from extracellular to intracellular compartments. In oncologic and malnourished patients, individuals at particular risk for developing refeeding syndrome, in the presence of these biochemical abnormalities, acute thiamine deficiency should be suspected and treated because it promptly responds to thiamine administration.

AM conceptualized and designed the study, carried out data collection and analyses, drafted the initial manuscript, and reviewed and approved the final manuscript as submitted. GV carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted. VC performed the data collection, participated in its design and coordination, and helped to draft the manuscript. ML performed the data collection, participated in its design and coordination, and approved the final manuscript as submitted. CR carried out the instrumental data analyses, participated in the interpretation of data and participated in its design and coordination, and helped to draft the manuscript. FE participated in its design and coordination, critically reviewed the manuscript, and approved the final manuscript as submitted. CDV designed the data collection instruments, coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted. All authors read and approved the final manuscript. The authors declare that they have no competing interests.

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Introduction

Thiamine deficiency can occur in anorexia nervosa, in leukemia/cancer [1], in patients receiving unsupplemented total parenteral nutrition (TPN) [2], in children fed with defective soy-based infant formulas [3], or in individuals who chronically abuse alcohol [4]. Clinical features of thiamine deficiency include neurologic, cardiovascular, and metabolic manifestations [2]. Furthermore, acute thiamine deficiency has been considered a component of refeeding syndrome (RS), a potentially lethal condition characterized by severe electrolyte and fluid imbalance [5]. RS was originally described in grossly malnourished prisoners released from concentration camps during World War II who presented with heart failure, neurologic complications with convulsions, and coma following refeeding [5,6]. RS characteristically occurs when malnourished and starved individuals receive high-carbohydrate feeding leading to a sudden change of the energy sources, from fat to carbohydrates, which causes a sustained increase in insulin secretion. The insulin action induces a sudden shift of salt from the extracellular to the intracellular compartment. The laboratory hallmark of RS is hypophosphatemia; additional features include reduced plasma potassium and magnesium levels, hyperglycemia, metabolic acidosis, along with sodium and water retention causing fluid overload [4,7,8]. The consequences of these severe changes can be life threatening. High-risk conditions include recent weight loss, secondary to poor caloric intake or nutrient losses [8]. Patients with malignancy are at particular risk for developing RS, because they frequently develop malnutrition and depletion of micronutrients and electrolytes as a consequence of their treatment. An excessive parenteral carbohydrate supply may act as a trigger for RS, especially if glucose supply is not adequately supplemented with vitamins and oligoelements [4, 9]. Interestingly, laboratory findings similar to RS are also observed in acute thiamine deficiency [1]. In this paper, we report on two children with leukemia who developed acute thiamine deficiency and showed an electrolyte pattern of RS, whose pathogenetic mechanism was due to a severe proximal renal tubular dysfunction that promptly responded to thiamine administration.

Case reports

Case 1

This infant presented at 5 mo of age with intestinal bleeding, severe anemia, and thrombocytopenia leading to the diagnosis of B-cell leukemia. She was enrolled in the International Collaborative Treatment Protocol for Children under 1 y of age (INTERFANT 2006). During the consolidation phase, a few days after the first administration of intravenous (IV) high-dose methotrexate 5000 mg/m^2, the child presented with diarrhea and vomiting treated by parenteral hydration with 5% glucose saline solution for 1 wk. Total parenteral nutrition (TPN) support with a glucose concentration of 33% was started on the following day (day 0), when a second dose of IV methotrexate 5000 mg/m^2 was administered. Feeding difficulties persisted and TPN was continued. On day 19, clinical conditions further deteriorated with appearance of tachypnea and lethargy. Blood gas analysis revealed severe metabolic acidosis (pH 6.9, normal value [nv] 7.32–7.48; base excess [BE] −25 mEq/L, nv −2/+3; HCO^{3-} 5 mEq/L), high anion gap (21 mEq/L), hyperlactatemia (13.3 mMol/L, nv 0.4–2.2, 120 mg/dL, nv 4–20), and moderate hyperglycemia (158 mg/dL). Further laboratory findings showed severe hypophosphatemia (0.9 mg/dL), hypokalemia (2.5 mEq/L), and hypomagnesemia (1.4 mg/dL). As shown in Table 1, mineral and electrolyte imbalance was consistent with proximal tubular dysfunction with renal loss of phosphate, magnesium, and potassium. Despite IV administration of large-dose bicarbonate, up to 10 mEq/kg, and electrolyte supplementation, clinical conditions and severe metabolic acidosis and electrolyte imbalance further deteriorated. Continuous veno-venous hemofiltration was started on day 20 but caused only slight improvement. On day 21, examination of urinary organic acids showed a characteristic pattern seen in thiamine deficiency [1] (Fig. 1). Soon after 300 mg thiamine administration, we observed an almost immediate improvement of clinical conditions with complete normalization of metabolic acidosis within 3 h (Fig. 2). In the following 24 to 48 h, blood electrolyte abnormalities fully recovered with normalization of blood lactate and urine organic acid profile. Proximal tubular dysfunction completely resolved in the following days (Table 1).

Table 1
Results of blood and urinary laboratory tests before and after thiamine administration

	HCO^{3-} (mEq/L)	AG (mEq/L)	Lactate (mMol/L)	Glycemia (mg/dL)	Na_s (mEq/L)	FeNa (%)	Mg_s (mEq/L)	FeMg (%)	P_s (mg/dL)	TRP (%)	K_s (mEq/L)	TTKG
Case 1												
Day 19	5 ↓	21 ↑	13.3	158 ↑	132 ↓	5 ↑	1.4 ↓	4.8 ↑	1.2 ↓	59 ↓	2.3 ↓	12.5 ↑
Day 20	11 ↓	35 ↑	14.4	137 ↑	135 ↓	11 ↑	1.2 ↓	8.6 ↑	0.9 ↓	40 ↓	2.8 ↓	20 ↑
Day 21	thiamine											
3h later	32 ↑	15										
Day 23			1.6	115	137		2		3.5		3.9	
Day 29				90	142	1	1.7	3	4	95	4	7.5
Case 2												
Day 19	3 ↓	35 ↑	15.5	270 ↑	134 ↓	10 ↑	1.2 ↓	5.2 ↑	1.2 ↓	65 ↓	2.5 ↓	20 ↑
Day 20	5 ↓	31 ↑	14.9	160 ↑	134 ↓	8 ↑	1.1 ↓	6.7 ↑	1.6 ↓	60 ↓	2.4 ↓	25 ↑
Day 21	thiamine											
3h later	37 ↑	14										
Day 23			2.2	99	136		1.6		3.3		3.6	
Day 29				90	142	1	1.7	3	4	95	4	7.5

AG, anion gap (nv 10-14) calculated by the formula Na – (HCO3- + Cl) (not corrected for abumin levels); FeMg, urinary fractional magnesium excretion (nv <4%); FeNa, urinary fractional sodium excretion (nv 1%); Glycemia, nv 60-110 mg/dl; HCO3, nv 19-27; Ks, serum potassium level (nv 3.5-5.1); Lactate, nv 0.4-2.2 mMol/L; Mgs, serum magnesium level (nv 1.7-2.3); Nas, serum sodium level (nv 136-145); Ps, serum phosphate level (nv 3-6); TRP, urinary fractional phosphate reabsorption (nv >85%); TTKG, trans-tubular potassium gradient (nv 6-11).

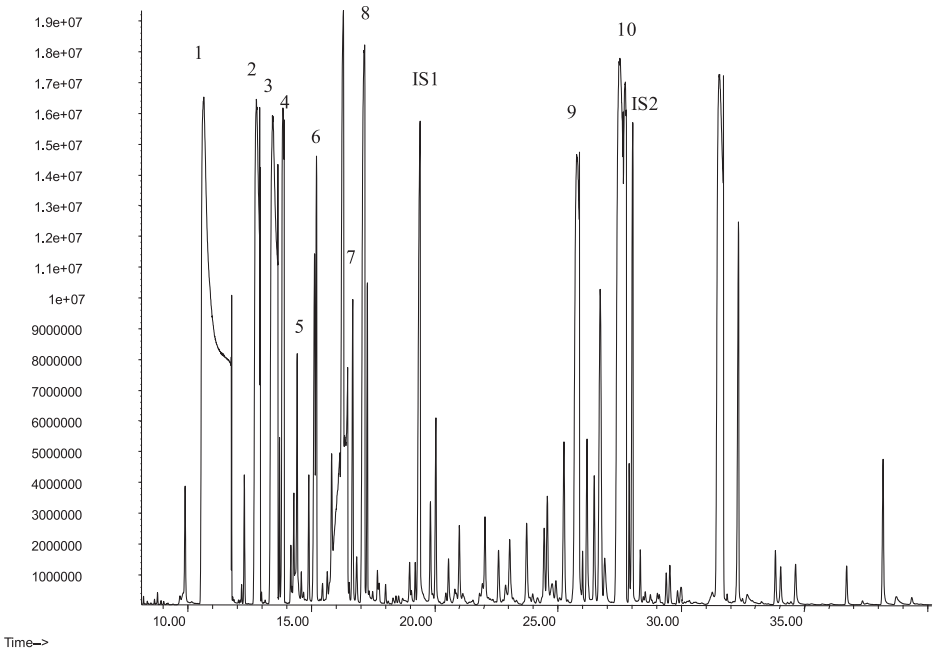

Fig. 1. Urinary organic acids profile in thiamine deficiency. Thiamine is a cofactor of piruvate dehydrogenase complex, 2-ketoglutarate dehydrogenase complex, and branched-chain α-ketoacid dehydrogenase complex. These enzymatic complexes catalyze the hydrolysis of the α-ketoacids, which enter the Krebs cycle for their complete oxidation and adenosine triphosphate generation. Thiamine deficiency provokes accumulation of urinary α-ketoacids along with lactate, pyruvate, 2-hydroxybutyrate and 2-hydroxyisovalerate. 1. lactic acid; 2. 2-OH-butyric acid; 3. pyruvic acid; 4. 2-OH-isovaleric acid; 5. 2-keto-butyric acid; 6. 2-keto-isovaleric acid; 7. 2-keto-3-methyl-valeric acid; 8. 2-keto-isocaproic acid; 9. 2-keto-glutaric acid; 10. 2-keto-adipic acid; IS1 (internal standard 1) 2-phenylbutyric acid; IS2 (internal standard 2) tricarballylic acid.

Case 2

This young boy was diagnosed with acute myeloid leukemia at the age of 9 y. He was enrolled in the Italian Protocol AIEOP LAM 2002. During the first chemotherapy course, he developed persistent vomiting requiring TPN with a 33% glucose concentration (day 0). On day 19, he suddenly developed mental status changes, hypothermia, hypotension, and tachypnea. Cerebral magnetic resonance imaging showed bilateral high-intensity signals of basal ganglia. Blood gas analysis revealed severe metabolic acidosis (pH 6.8; BE −29 mEq/L; HCO^{3-} 3 mEq/L; anion gap 35 mEq/L), hyperlactatemia (15.5 mMol/L, 140 mg/dL), and hyperglycemia (270 mg/dL). Further laboratory findings showed hypophosphatemia (1.2 mg/dL), hypokalemia (2.4 mEq/L), and hypomagnesemia (1.2 mg/dL). Similar to patient 1, urinary investigation showed evidence of proximal renal tubular dysfunction (Table 1). Attempts to correct metabolic acidosis with IV sodium bicarbonate were ineffective. Reviewing of his TPN prescription showed that vitamin supplementation was missed. Thiamine deficiency was confirmed by analysis of plasma levels (30 nmol/L, nv 66.5–200) and by analysis of urinary organic acids, which showed a characteristic profile. Three hours after administration of 300 mg thiamine, metabolic acidosis disappeared; electrolyte abnormalities and renal tubular function fully recovered within 5 d (Table 1).

Discussion

Malnourished patients presenting with acute illnesses receiving parenteral hydration with high-concentration glucose solutions or treated with enteral or parenteral nutrition without adequate vitamin supplementation, are at high risk for developing RS [1,5,7,10,11]. Thiamine deficiency, which often is listed among the causes of RS, may cause metabolic, neurologic and cardiovascular symptoms, similar to RS [12]. As frequently observed in children with leukemia receiving chemotherapy, the two patients discussed here presented with severe and

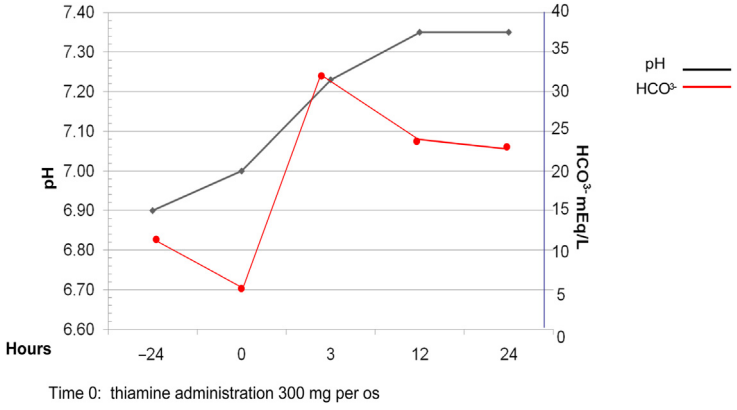

Fig. 2. Early effect of thiamine administration on metabolic acidosis. Plasma pH and bicarbonates returned to normal within 3 h from thiamine administration.

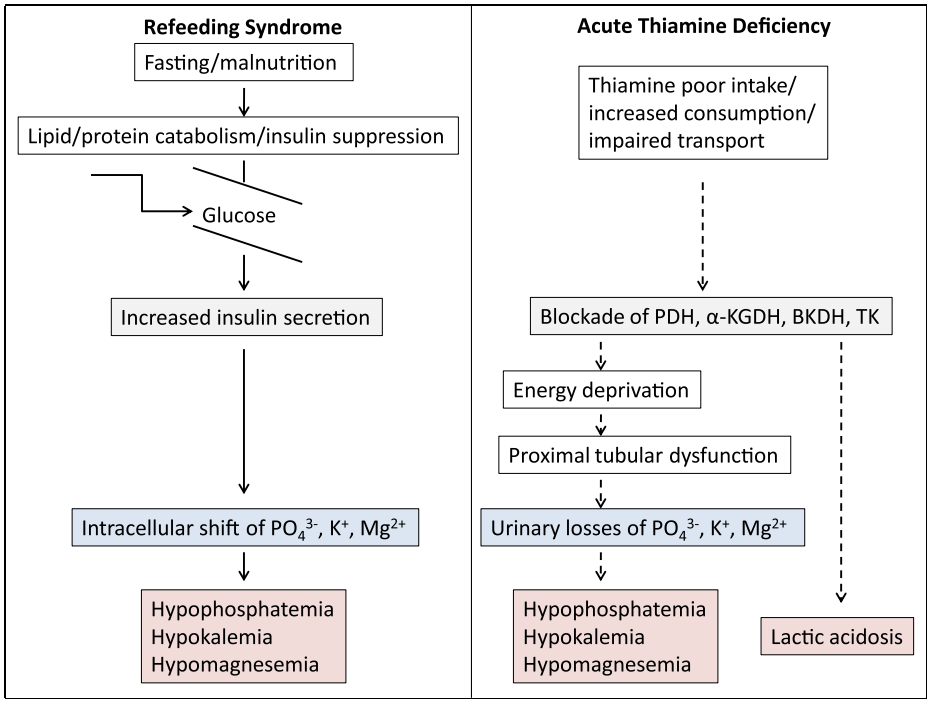

Fig. 3. Speculative mechanisms of intracellular plasma electrolytes depletion. In *continuous lines*, electrolytes imbalance is explained as intracellular shift of electrolytes caused by the action of insulin, acutely released after carbohydrate administration. In *dotted lines*, thiamine deficiency provokes Krebs cycle impairment in tubular cells with metabolic acidosis and urinary losses of electrolytes. α-KGDH, α-ketoglutarate dehydrogenase; BKDH, branched chain α-ketoacids dehydrogenase; PDH, piruvate dehydrogenase; TK, transketolase.

protracted gastrointestinal signs with poor food intake before manifesting acute thiamine deficiency. Additionally, one was treated with high doses of methotrexate, a drug that competes with cell thiamine transport systems [13], and the second erroneously received unsupplemented TPN. Thiamine deficiency was confirmed by serum thiamine measurement in one patient and by the finding of characteristic metabolic changes in both children (i.e., lactic acidosis combined with a specific urine organic acids profile). In addition to these changes, both patients showed an electrolyte pattern in blood very similar to what is observed in RS [10,11]. During refeeding, carbohydrate intake stimulates insulin secretion and reverts catabolism to anabolism, creating a sudden demand of inorganic phosphate for synthesis of adenosine triphosphate (ATP), potassium for intracellular glucose transport, magnesium for synthesis reactions, and thiamine for carbohydrate and amino acid oxidation [9]. Interestingly, similar electrolyte disturbances can be observed in patients with poorly controlled diabetes mellitus, a condition with low insulin levels [14], suggesting that alternative mechanisms can be responsible for these electrolyte imbalances. Our patients showed clear evidence of severe renal tubular dysfunction, causing urinary losses of phosphate, potassium, and magnesium. Hypokalemia [1,10] and hypophosphatemia [1] have been reported in patients with lactic acidosis due to thiamine deficiency; however, tubular function has not been investigated in these cases [1]. In thiamine deficiency, the cytosolic conversion of pyruvate into lactate by anaerobic metabolism causes lactic acidosis. The presence of hypophosphatemia, hypokalemia, and hypomagnesemia in our patients therefore can be interpreted as the consequence of energy deprivation affecting renal tubular cells.

Thiamine is not stored in appreciable amounts in cells, has a short half-life, and cell stores are usually depleted within 20 d of malnutrition [12]. Abrupt increase of carbohydrate oxidation may precipitate acute deficiency because it accelerates the consumption of residual thiamine stores [4]. Remarkably, our patients developed acute thiamine deficiency approximately 20 d after starting TPN. One patient's TPN did not include vitamin supplementation, whereas the TPN of the patient receiving high-dose methotrexate contained a standard thiamine dose, which is approximately 100 times lower than the amount required in the case of thiamine deficiency [12].

Thiamine is the cofactor of pyruvate dehydrogenase, branched-chain α-ketoacids dehydrogenase, transketolase, and α-ketoglutarate dehydrogenase. These enzymes are involved in acetyl coenzyme A formation, in branched-chain amino acid catabolism, in connecting the pentose phosphate pathway to glycolysis, and in Krebs cycle, respectively. When thiamine is deficient, a combined enzymatic defect occurs, as reflected in the characteristic organic acid pattern [1], causing Krebs cycle and ATP synthesis impairment [12]. In this view, thiamine deficiency may cause disruption of renal tubular function, resulting in decreased reabsorption of electrolytes as a consequence of impaired tubular ATP-dependent transport systems [15,16]. The dramatic response to a single thiamine dose supports this concept. Through transketolase activity, thiamine plays a pivotal role in protecting against oxidative stress [17,18], thus in thiamine deficiency the insufficient ATP generation combined with toxic effects of reactive oxygen species can lead to acute tubular necrosis through an ischemia-reperfusion injury [19]. Therefore, it can be concluded that the urinary electrolyte losses in our patients is the result of an early phase of tubular impairment caused by thiamine deficiency. Not surprisingly, the most frequent renal finding in disorders of mitochondrial oxidative phosphorylation is a proximal tubular defect [20,21]. Interestingly, the development of acute tubular necrosis has been described as part of a RS

in one patient [22]. Our report indicates that, despite sharing many laboratory similarities, RS and acute thiamine deficiency should be viewed as separate entities. It is possible that electrolyte abnormalities reported in cases of RS with thiamine deficiency and refractory lactic acidosis may be the result of renal tubular losses instead of a shifting from extracellular to intracellular compartment. In this view, hypophosphatemia, hypokalemia, and hypomagnesemia in RS without lactic acidosis are most likely caused by an imbalance between intra- and extracellular compartments, whereas in the presence of lactic acidosis these changes are more likely secondary to renal tubular losses caused by thiamine deficiency (Fig. 3). Many reports concerning thiamine deficiency and development of refractory lactic acidosis along with neurologic, cardiovascular, and intestinal manifestations are described (Supplementary Table 1). Therefore, when such conditions are associated with severe lactic acidosis, a thiamine deficiency should be suspected.

Conclusion

Oncologic and malnourished patients should be carefully monitored to avoid severe electrolyte abnormalities related to thiamine deficiency, a life-threatening condition that, if promptly recognized, dramatically responds to thiamine administration. However, further studies with more patients are necessary to support our findings.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.nut.2014.02.019.

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