INDEX OF SUSPICION

Persistent Lactic Acidosis in an 18-month-old Girl Status Post Bone Marrow Transplant

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PRESENTATION

An 18-month-old girl with juvenile myelomonocytic leukemia develops lactic acidosis. She was diagnosed with juvenile myelomonocytic leukemia at 14 months old and received a bone marrow transplant (BMT) at 17 months of age.

The hospital course is complicated by severe anorexia, and enteral intake is limited to minimal human milk. On day 1 after BMT, she begins on total parenteral nutrition (TPN) with intravenous (IV) multivitamins and intralipids (IL). On day 11 of TPN/IL, she develops hives and emesis coinciding with start of the TPN/IL infusion, concerning for an allergy. The next day, TPN alone is administered and tolerated. When IL is reintroduced, she again develops hives. Allergy consultants review the case, and diagnose an allergy to IL. Exclusive TPN is continued, without multivitamins/IL, for 4 weeks.

On day 20 post-BMT, she begins to take an oral multivitamin. Multiple attempts at enteral feeds have occurred, but she has emesis, food refusal, and gut graft-versus-host disease. On day 46, she develops tachycardia and tachypnea. Laboratory testing reveals metabolic acidosis with a bicarbonate level of 14 mmol/L with anion gap 25, and an elevated lactate level of 11.5 mmol/L. Pyruvate is also elevated, at 0.45 mmol/L (normal 0.05 to 0.14 mmol/L). She is treated empirically for sepsis, but cultures are negative and lactate remains persistently elevated. Subsequent testing reveals the cause for the persistently elevated lactate level.

DISCUSSION

Review of the patient's nutritional history led to concerns for exogenous causes of lactic acidosis, such as thiamine deficiency. Thus, thiamine levels were sent and found to be less than 2 nmol/L (normal 8 to 30 nmol/L). IV thiamine supplementation was started. However, lacticemia persisted over the next 4 days (range: 2.0 to 11.5 mmol/L). Metabolism was then consulted and reviewed the timeline of her nutritional history, which raised concern for multiple vitamin deficiencies. Further vitamin and nutritional element testing was done. The patient's laboratory results revealed not only multiple vitamin deficiencies (Table 1), but also dysfunction of multiple metabolic pathways mimicking inborn errors of metabolism, underscoring the important role that vitamins play in human metabolism.

AUTHOR DISCLOSURE Drs Murali and Ganetzky have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. Patient's Vitamin Levels and Normal Ranges

VITAMIN	LEVEL IN PATIENT	NORMAL RANGE
B_1 (thiamine)	<2 nmol/L	8–30 nmol/L
B_2 (riboflavin)	3 nmol/L	5–50 nmol/L
B_3 (niacin)	0.67 μg/mL (2.48 μmol/L)	0.50–8.91 μg/mL (1.85–32.97 μmol/L)
B_6 (pyridoxine)	12.8 nmol/L	20.0–125.0 nmol/L
B_9 (folic acid)	1.5 ng/mL (3.4 nmol/L)	6.3–22.7 ng/mL (14.3–51.4 nmol/L)
Methylmalonic acid (proxy for B_{12})	137 nmol/L	100–370 nmol/L
C	<5 μmol/L	23–114 μmol/L
D (25-OH)	20.30 ng/mL (20.30 μg/L)	>20 ng/mL (>20 μg/L)

Laboratory Results

As mentioned, thiamine (vitamin B_1) deficiency is a known cause of lactic acidosis. The pathogenic mechanism is through decreased function of pyruvate dehydrogenase, for which thiamine pyrophosphate acts as a cofactor, a role it performs for all α-ketoacid dehydrogenases in the body (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, branched chain α-ketoacid dehydrogenase). The patient's thiamine deficiency was reflected in her elevations in both lactate and pyruvate. Pyruvate is elevated only when there is dysfunction in pyruvate metabolism (as opposed to electron transport chain defects, or systemic causes for lactic acidosis). The low thiamine level also caused dysfunction of branched chain α-ketoacid dehydrogenase, evidenced by her elevated levels of valine, isoleucine, and leucine on plasma amino acids. Alloisoleucine was not detected.

Two enzymatic reactions convert pyruvate into molecules that can enter the citric acid cycle: pyruvate dehydrogenase, for which thiamine is a cofactor, and pyruvate carboxylase, for which biotin is a cofactor. Though biotin levels cannot be directly measured, they can be inferred from organic acid testing. In addition to pyruvate carboxylase, biotin acts as a cofactor for all carboxylase reactions, including 3-methylcrotonyl-coenzyme A (CoA) carboxylase, which is involved in leucine metabolism. The patient's urine organic acids revealed dysfunction of this enzyme, with elevations of 3-hydroxy-isovaleric acid and 3-methylcrotonyl glycine. Additionally, the patient's persistent lacticemia despite thiamine repletion further underscored that biotin deficiency was present and contributed to her presentation.

Her riboflavin level was measured and low, which was reflected by a pattern of metabolic abnormalities consistent with multiple acyl-CoA dehydrogenase deficiency. Acyl-CoA dehydrogenases are a family of enzymes involved in fatty acid and amino acid metabolism, all of which require riboflavin as a cofactor. Specifically, her urine organic acids showed elevations in organic acids derived from amino acids: isobutyryl glycine (reflects isobutyryl-CoA dehydrogenase deficiency),

TABLE 2. List of All Metabolic Abnormalities Mimicking Inborn Errors of Metabolism in the Patient, the Enzymes Responsible for These Errors of Metabolism, the Vitamin Cofactor, and the Elevated Biochemical Markers

INBORN ERROR OF METABOLISM	ENZYME	VITAMIN COFACTOR	BIOCHEMICAL MARKER
3-MCC deficiency	3-methylcrotonyl-CoA carboxylase	Biotin	3-hydroxyisovaleric acid 3-methylcrotonylglycine
Pyruvate carboxylase deficiency	Pyruvate carboxylase	Biotin	Lactate Pyruvate
Maple syrup urine disease	Branched chain ketoacid dehydrogenase	Thiamine	Valine Isoleucine Leucine
Pyruvate dehydrogenase deficiency	Pyruvate dehydrogenase	Thiamine	Lactate pyruvate
MCAD deficiency	Medium chain acyl-CoA dehydrogenase	Riboflavin	Suberylglycine Hexanoylglycine
Isovaleric acidemia	Isovaleryl-CoA dehydrogenase	Riboflavin	Isovalerylglycine
Isobutyric academia	Isobutyryl-CoA Dehydrogenase	Riboflavin	Isobutyrylglycine

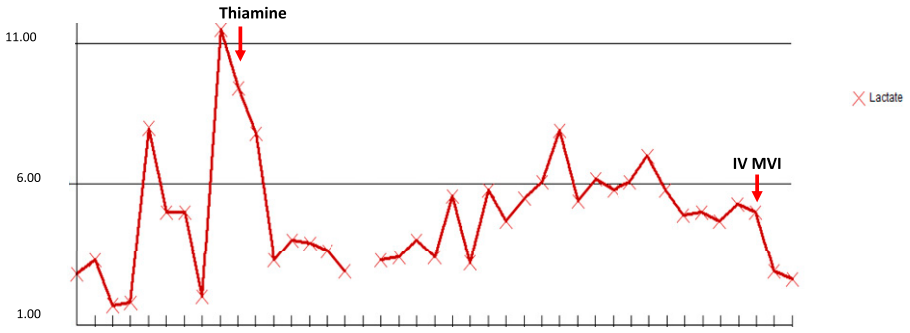

Figure 1. Patient's lactate levels before and after administration of thiamine and IV multivitamin containing biotin and riboflavin.

isovaleryl glycine (isovaleryl-CoA dehydrogenase deficiency); and from fatty acids: hexanoyl glycine and suberyl glycine (medium chain acyl-CoA dehydrogenase deficiency).

Carnitine is present in foods derived from animal sources, including meats, dairy, and breastmilk. It can be administered in IV form along with TPN, but the patient was not receiving IV carnitine. The patient's free carnitine level was low, which reflected not only the lack of IV carnitine administration but also the lack of gut absorption of orally ingested breast milk. This value highlighted the severity of her gut graft-versus-host disease and implied that she was not absorbing nutrition from the oral multivitamin.

In all, the patient's biochemical testing revealed dysfunction of numerous metabolic pathways, which was due to abnormally low vitamin levels (Table 2). Vitamins are essential cofactors for multiple biochemical pathways. This case underscores the importance of complete, balanced nutrition in pediatric patients, especially those with chronic illness. Inadequate intake of vitamins can result in severely deranged metabolism. Indeed, poor nutritional health can mimic multiple inborn errors of metabolism.

Management

Once the diagnosis of thiamine deficiency was confirmed, the patient was immediately started on IV thiamine therapy, before consultation with metabolic specialists. Her lactate levels initially responded well, returning to normal levels. However, lactate levels subsequently rose once more.

Administration of thiamine addressed dysfunction in pyruvate dehydrogenase, but metabolic consultants found that the patient also had evidence of biotin deficiency, which causes secondary dysfunction of pyruvate carboxylase, and riboflavin deficiency, which results in secondary fatty acid oxidation dysfunction and mitochondrial complex II dysfunction. Therefore, IV biotin and riboflavin were subsequently administered in the form of an IV multivitamin, which resulted in normalization of lactate levels to 1.6 mmol/L 3 weeks after initiation (Fig 1).

Additionally, the patient received full IV repletion of other deficient vitamins and minerals (vitamin D, copper, selenium, zinc, folate, and vitamin C). Trace elements were added back to her IV nutrition. Upon review of her multiple reactions (hives, emesis, itchiness), allergy consultants concluded that they were likely secondary to the IL portion of her TPN. She was initiated on a fatty acid emulsion rich in Ω-3 acids and tolerated it well without any concerns for allergic reaction. Since the time of initial presentation with lactic acidosis, there have been intermittent elevations in lactate levels; however, all have been directly attributable to clinical status (eg, postsurgical), and baseline lactate levels have remained normal.

Lessons for the Clinician

- Thiamine deficiency and biotin deficiency can directly cause lactic acidosis through inhibition of pyruvate dehydrogenase and pyruvate carboxylase reactions, respectively.
- Riboflavin deficiency can cause secondary lactic acidosis through inhibition of fatty acid oxidation and mitochondrial complex II dysfunction.
- Vitamins are cofactors for many metabolic reactions.
- Vitamin deficiency can mimic inborn errors of metabolism.
- In the setting of proportionally elevated pyruvate, lactic acidosis is due to disruption in pyruvate metabolism.

References for this article can be found at http://pedsinreview.aappublications.org/content/41/No. S1/S20.

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