Severe Lactic Acidosis in a Critically Ill Child: Think About Thiamine! A Case Report

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Abstract

In this article, we presented a teenager, in maintenance chemotherapy for leukemia, who was admitted for digestive symptoms related to a parasitic infection and required nutritional support with parenteral nutrition. After 6 weeks, his condition worsened with refractory shock of presumed septic origin, necessitating extracorporeal membrane oxygenation. Despite hemodynamic stabilization, his lactic acidosis worsened until thiamine supplementation was started. Lactate normalized within 12 hours. Thiamine is an essential coenzyme in aerobic glycolysis, and deficiency leads to lactate accumulation through anaerobic glycolysis. Thiamine deficiency is uncommon in the pediatric population. However, it should be considered in patients at risk of nutritional deficiencies with lactic acidosis of unknown origin.

Keywords

- ▶ lactic acidosis
- ▶ critically ill child
- ▶ thiamine deficiency

Introduction

Lactic acidosis in the critically ill is a warning sign for clinicians as it often results from hypoxemia and tissue hypoperfusion. However, those are not the only etiologies and other less frequent diagnoses should not be forgotten, such as thiamine deficiency.

Thiamine, or vitamin B1, is a water-soluble vitamin essential for carbohydrate metabolism.^{1,2} It is found in various nutriment, and is both passively and actively absorbed in the small intestine. It is then converted to thiamine pyrophosphate, an essential coenzyme for different metabolic pathways, especially for the mitochondrial enzyme pyruvate dehydrogenase (PDH). PDH allows pyruvate to enter the Krebs cycle by transforming it into acetyl coenzyme A, leading to adenosine triphosphate production. In the case of thiamine deficiency, pyruvate is degraded by anaerobic metabolism, resulting in lactate formation and accumulation.

A review of Collie et al highlights the lack of standardized procedures for thiamine measurements in blood.² In addition,

current literature data does not agree on reference intervals for thiamine values of clinical pertinence in adults, and there is even less data published on the pediatric population. As a result, the comparison between different published studies is difficult.

Despite the absence of consensus on reference values, thiamine deficiency has been related with different clinical presentations.³ The most notable form is Beriberi disease with its “dry” neurologic form (including Wernicke’s encephalopathy) and the “wet” cardiologic form, culminating in acute Shoshin beriberi. Thiamine deficiency has been reported as the etiology for acute cardiac failure presenting as cardiogenic shock in different case reports.^{4–6} Acute thiamine deficiency has also been associated with other lesser known presentations including, as in our case and others described below, lactic acidosis.

We reported the case of a teenager, known for acute lymphoblastic leukemia, transferred to the pediatric intensive care unit (PICU) with shock of presumed septic origin. He needed extracorporeal membrane oxygenation (ECMO) therapy for cardiorespiratory failure due to an acute respiratory

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distress syndrome. Despite appropriate hemodynamic and respiratory support, his severe lactic acidosis persisted but resolved rapidly after intravenous thiamine supplementation.

Case Report

A 13-year-old male patient, with acute lymphoblastic leukemia in the maintenance phase of treatment, was admitted to our PICU for a shock of presumed septic origin. In the past 3 months, he presented digestive symptoms (vomiting, diarrhea, and loss of appetite) and fatigue. An infection with cryptosporidium had been diagnosed, leading to discontinuation of his oncologic treatment and introduction of anti-parasitic treatment with nitazoxanide. Due to persistent gastrointestinal tract symptoms, poor oral intake, and early signs of malnutrition, parenteral nutrition was started 6 weeks prior to his admission to the PICU to cover his metabolic needs at rest. On the days preceding his transfer, he presented with persistent tachycardia, worsening digestive symptoms with severe aqueous diarrhea and vomiting as well as pancytopenia. Fearing a relapse of his leukemia, a bone marrow evaluation was performed under general anesthesia. During the intervention, he became febrile and hypotensive and required transfer to PICU.

On arrival to the PICU, he complained about worsening abdominal pain. He was febrile and hemodynamically unstable requiring vasopressor support with norepinephrine. Venous blood gas showed a partially compensated metabolic acidosis with lactic acidosis (pH = 7.23, pCO₂ = 33.5 mm Hg, pO₂ = 36.5 mm Hg, bicarbonates = 15 mmol/L, and lactate = 8.9 mmol/L). Acute pancreatitis was excluded on computed tomography (CT) and laboratory evaluation. Based on the CT scan, an intestinal perforation was initially suspected but was excluded by laparotomy. The patient further deteriorat-

ed with ongoing refractory hypoxemia and hypotension despite maximal vasopressor support. The decision for introduction of extra-cardiac life support was made, and central veno-arterial ECMO was started 26 hours after admission. The patient's response was initially favorable with an improvement of oxygenation and hemodynamic stabilization, allowing weaning of vasopressin and adrenaline in the following 30 hours. A peak arterial blood lactate of 19.6 mmol/L was measured just after ECMO therapy institution and then dropped rapidly. However, it remained above 7 mmol/L and increased again up to 16.7 mmol/L with metabolic acidosis after 70 hours on ECMO.

The patient showed no clinical signs of hypoperfusion, was hemodynamically stable with need of minimal aminergic support. A new abdominal CT scan again excluded ischemic bowel injury. Hypoxic etiologies appeared unlikely. Increased lactate production caused by convulsions or high fever was excluded. Tumor necrosis—another cause of increased lactate production—had been ruled out by bone marrow evaluation, showing no signs of leukemia relapse. A review of the administered drugs did not reveal any support in favor of a toxic origin. An underlying metabolic dysfunction was suspected. Liver function was normal. Due to age and the patient's history, a mitochondrial disease seemed unlikely. Thiamine deficiency was then suspected, and a blood sample was taken for analysis of thiamine concentration. Thiamine supplementation was started empirically with a dose of 100 mg IV (Benerva; Farmaceutica Teoforma, Switzerland), followed by a multivitamin preparation once daily (with 3.51 mg of thiamine/day, Cernavit; Baxter AG, Switzerland).

Following thiamine administration, lactate levels dropped dramatically over the next 12 hours to 2.6 mmol/L and remained below 2 mmol/L for the rest of the hospitalization (► Fig. 1). The clinical progress of the patient was favorable,

Fig. 1 Lactate level (mmol/L) evolution in the hours following admission, with two peak values: 19.6 mmol/L at H16 and 16.7 mmol/L at H82. The first one is followed by a decrease following extracorporeal membrane oxygenation (ECMO) Therapy. The second one is followed by a dramatic drop all the way to normal values after thiamine administration.

allowing withdrawal of ECMO after 18 days. After a slow respiratory recovery, he was transferred to the pediatric ward. He returned home 3 months after admission to PICU.

When his medical record was reviewed, it was realized that the patient never received any vitamin supplementation while on parenteral nutrition, resulting in insufficient nutritional thiamine intake. This error may have been caused by the fact that parenteral nutrition was added only as a supplementation to his oral intake. However, his severe digestive symptoms probably lead to poor gastrointestinal absorption, malnutrition, and subsequent thiamine deficiency.

The patient's blood thiamine level was in the lower range of normal values for our laboratory (70.7 nmol/L, laboratory normal values: 60–200 nmol/L).

Given the dramatic decrease of blood lactate following thiamine administration without other therapeutic changes, thiamine deficiency remains the only plausible etiology for the lactic acidosis.

Discussion

For clinicians, and particularly intensivists, lactic acidosis is primarily a reflection of tissue hypoxia, caused by low cardiac output, hypoxemia, or sepsis. In these situations, clinical features such as oliguria, hypotension, and tachycardia suggest a state of shock. However, if the patient's clinical condition remains stable, other causes of lactic acidosis should be considered as illustrated by this case. Thiamine deficiency should be considered, especially in high-risk patients, even in children.

Thiamine deficiency is reported in adult literature as a cause for unexplained lactic acidosis, being mainly linked to alcohol abuse^{7,8} or parenteral nutrition without vitamins.^{9,10} Thiamine deficiency must be suspected in certain clinical situations, such as malnutrition, alcoholism, malignancy, and burns.¹¹ Critically ill patients are particularly at risk. In pediatrics, routine thiamine supplementation for deficiency is rare and pediatricians might underestimate conditions that can lead to thiamine deficiency. However, deficient intake leading to symptomatic thiamine deficiency is possible, even in developed countries as reported by Fattal-Valevski et al.¹² They describe nine infants from Israel, hospitalized for digestive (vomiting, constipation, lack of appetite, etc.) and neurological (apathy, convulsions, etc.) symptoms as well as lactic acidosis. All these children were fed by the same soy-based formula, which did not contain thiamine due to a manufacturing problem.

A few authors also reported rapidly disappearing lactic acidosis after thiamine administration in pediatric patients, most linked to parenteral nutrition without vitamin supplementation, and some in hematologic context.^{13–15} Teagarden et al reported a neonate with malignant pertussis on ECMO support and continuous renal replacement therapy (CRRT), who after 9 days developed a new lactic acidosis.¹⁶ Like in our case, there was a discrepancy between the clinical stability of the patient under ECMO and CRRT therapy and blood laboratory results. In this case, thiamine supplementation had been forgotten in a total parenteral nutrition and thiamine supplementation rapidly cleared lactic acidosis.

Lactic acidosis without tissue hypoxemia in hemato-oncologic diseases has also been reported.¹⁷ The origin appears to be multifactorial and a poor prognostic factor.¹⁸ In a 2007 review, Friedenberget al¹⁷ reported 7 adult cases of lactic acidosis from their institution and 14 from the literature. Interestingly, among 14, four were pediatric patients and three of which were linked to thiamine deficiency and resolved after thiamine supplementation. Hemato-oncologic disease seems to be a risk factor for thiamine deficiency, often subclinical, and of uncertain origin.¹⁹ In our patient, it was initially feared that a relapse of his leukemia could play a role in his lactic acidosis. However, a bone marrow biopsy done hours prior to his ICU admission was negative for recurrence. His thiamine deficiency and resulting lactic acidosis were therefore not linked to oncologic pathology but most likely to malabsorption and parenteral nutrition without supplementation.

The prevalence of thiamine deficiency in ICU patients is not known, and the literature is scarce. Donnino et al²⁰ reported thiamine deficiency at entry into intensive care in 10% (cohort of 30 patients) of adult patients hospitalized for sepsis. Total 72 hours after admission, 20% of patients were deficient. Despite these results only, one patient received thiamine supplementation in this study. A study of 202 children admitted to PICU in Brazil showed a thiamine deficiency (blood thiamine < 47 nmol/L) in 30.2% of children, without correlation to their nutritional status.²¹ A recent review by Attaluri et al²² highlighted not only the increased risk of thiamine deficiency in intensive care unit patients, but also the risk of developing thiamine deficiency during hospitalization as in the Teagarden case report.

Several teams tried to highlight the effect of thiamine on the outcome of intensive care patients. In a double-blinded randomized control trial, patients admitted for septic shock with lactate levels > 3 mmol/L and thiamine deficiency on admission presented with a greater decrease in lactate in the first 24 hours when receiving thiamine supplementation rather than placebo. This difference was not found for patients with no thiamine deficiency.²³

A team in São Paulo evaluated the correlation between thiamine levels and 30-day mortality in critically ill children.²⁴ In the malnourished patients (46%), a high blood thiamine level on admission was associated with a decreased risk of mortality. This correlation was not found in children with normal nutritional status.

Apart from malnutrition, vitamin deficiency can also arise from the often-overlooked problem of malabsorption, as highlighted by this case. Greenspon et al reported a child with short bowel syndrome on enteral vitamin supplementation who presented with hemodynamic instability and abdominal pain mimicking septic shock.²⁵ In this patient, not only lactate levels dropped after thiamine supplementation, but also vasopressor support could be quickly withdrawn. The authors attributed the hemodynamic instability to thiamine deficiency due to malabsorption and diagnosed Shoshin beriberi syndrome.

This raises the question of the implication of thiamine deficiency in our patient's hemodynamic state and

abdominal presentation. It is possible that—as in the case of Greenspon—thiamine deficiency played a role in the initial presentation of the patient, with a form similar to Shoshin beriberi syndrome, but this could not be fully ascertained.

At last, we would like to comment on thiamine blood level in our patient, which was within the lower standard of our laboratory. As mentioned above, there is no standard in thiamine measurements, and no standard references for pediatric patients or critically ill patients. But as described by Giacalone et al,⁹ the rapid decrease in lactic acidosis after administration of thiamine in our patient—without further modification of management—suggests a clinically significant deficit in thiamine despite the laboratory value.

Conclusion

Thiamine deficiency must be part of the differential diagnosis of unexplained lactic acidosis in adults and children. Clinicians need to know the factors that favor this entity, especially in critically ill or malnourished patients. Treatment is simple, safe, and may result in rapid decrease of the lactate levels.

This case illustrated that thiamine deficiency can lead to life-threatening complications. Its impact is still not very well known by clinicians, especially in pediatric clinics where it is not routinely supplemented. More studies are needed to validate methods for thiamine measurements and validate age-dependent reference ranges. The effects of thiamine supplementation in critically ill children on the short-, mid-, and long-term outcome deserve further investigations.

Conflict of Interest

None declared.

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