Pulmonary hypertension: A rare Presentation of thiamine deficiency in infancy

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Abstract
Persistent pulmonary hypertension (PPHN) is seen in approximately 10% of infants with respiratory failure with significant mortality and morbidity. Pulmonary hypertension in infants can be idiopathic, associated with vascular or parenchymal diseases. Thiamine deficiency is one of the reversible causes of pulmonary hypertension. 7 month old male infant presented with cough, fast breathing, decreased oral acceptance and excessive irritability. Echocardiography was suggestive of severe pulmonary hypertension without any structural heart disease. Rapid progression, history of exclusive breast feeding, persisting lactic acidosis prompted us to investigate for thiamine deficiency. Low blood thiamine levels confirmed the diagnosis. It was further confirmed by thiamine challenge (IV thiamine for 5 days) with rapid clinical improvement. Mother was also found thiamine deficient, started on oral supplements. Hence thiamine deficiency should be considered in all infants with pulmonary hypertension of unknown origin.

Keywords: Exclusive breastfeeding, pulmonary hypertension, thiamine challenge, thiamine deficiency

INTRODUCTION
Pulmonary hypertension in children has a varied clinical presentation and a heterogeneous etiology. In recent years, an increasing number of children with pulmonary hypertension have been associated with bronchopulmonary dysplasia, congenital diaphragmatic hernia, and sickle cell disease.[1] The idiopathic form of the disease, known as idiopathic PAH, complicates the course of approximately 10% of infants with respiratory failure, leading to considerable mortality and morbidity.[2]

Noninvasive measurement of pulmonary artery systolic pressure with echocardiography (ECHO) has made the diagnosis much easier. Thiamine deficiency (TD) is usually not assumed to be a common cause of isolated pulmonary hypertension. TD has been appropriately designated as “a rapidly curable hemodynamic disaster” with an extremely high mortality if not treated early.[3]

The present case highlights reversible pulmonary hypertension as a potentially common but possibly underdiagnosed manifestation of TD.

CASE REPORT
A 7-month-old exclusively breastfed male infant (weight 6.1 kg and length 55 cm) presented with cough and fast breathing for 2 days and decreased acceptance and excessive irritability...
for 1 day. There were no previous complaints, history of any drug intake (diuretics), diarrhea, and weight loss. Physical examination revealed tachycardia, gallop rhythm, and bilateral coarse crepitus. The liver was palpable 4 cm below the right costal margin, spanning 13 cm. His vitals were as follows: heart rate was 198/min (sinus), pulses were feeble, capillary filling time (CFT) was borderline, noninvasive blood pressure was 58/32 (40 mm of Hg), and body temperature was 99°F. The respiratory rate was 74 breaths/min with oxygen saturation of 86% while breathing 6 L/min of oxygen via a reservoir mask. Given these findings, he was admitted to the pediatric intensive care unit (PICU). In view of progressively increasing work of breathing and desaturations, the baby was intubated after a brief trial of noninvasive ventilation (AIRVO™, Fisher and Paykel Healthcare Corporation Limited).

Complete hemogram was 7.8/23.2/8000/N 38 L 57/5.2 lakhs. Rest of the blood investigation (liver function test, serum lactate, serum ammonia, Vitamin D, thyroid profile, and calcium levels) were within normal limits. Peripheral smear revealed microcytosis and anisopoikilocytosis. Chest X-ray showed increased bronchovascular markings with cardiothoracic ratio of 0.65. Electrocardiogram revealed normal sinus rhythm with right ventricular hypertrophy. Negative T wave in leads V3–V5 was suggestive of strain pattern. ECHO showed right ventricular dilatation with severe tricuspid regurgitation (TR). Two-dimensional ECHO revealed TR jet of 4.4 m/s. The estimated systolic pulmonary artery pressure as determined on continuous-wave Doppler ECHO was 80 mmHg; tricuspid annular plane systolic excursion of 7 mm, interventricular septal flattening with paradoxical motion, and inferior vena cava dilatation with hepatic vein dilation were suggestive of right ventricular dysfunction [Figures 1 and 2]. Computed tomography pulmonary angiography showed normal pulmonary parenchyma and vasculature. Serial blood gases depicted lactic acidosis persisting even after improving hemodynamics [Figure 3]. Pulmonary hypertension, lactic acidosis, sudden onset with rapid progression of symptoms, and poor initial response to therapy in an exclusively breastfed baby prompted us to suspect “thiamine deficiency.” The thiamine concentration in the whole blood (sampled on day 2) was 12 nmol/L (reference range 75–185 nmol/L). The mother’s whole-blood thiamine level was 25 nmol/L.

Intravenous (IV) thiamine (100 mg/day infusion over 30 min, once a day) was started on day 3, was continued for 5 days, and was subsequently shifted to oral route (50 mg twice a day). He was started on injection dobutamine, injection sildenafil, injection frusemide, and injection noradrenaline. The baby was ventilated for 4 days and was kept on high-frequency oscillatory ventilation for 3 days. Subsequently, injection milrinone was added. ECHO on extubation revealed mild elevation of pulmonary pressures and TR gradient of 27 mmHg [Figure 4]. He was continued on tablet sildenafil. ECHO at discharge revealed normal pulmonary pressures. On day 10, he had no symptoms or signs of heart failure and was discharged. Complementary feeds were started. Tablet sildenafil was stopped at discharge.

Thiamine supplementation was continued for 1 month for the baby, till the period of breastfeeding for the mother. The patient was followed up for 3 months. ECHO revealed normal pulmonary pressure.

**DISCUSSION**

Thiamine (Vitamin B1) is involved in the metabolism of carbohydrate and branched-chain amino acid, immune,
anti-inflammatory processes and gene regulation as well as in the production of neurotransmitters, myelin, and nucleic acids. Being an essential micronutrient, (no endogenous synthesis) body’s requirements are entirely dependent on dietary supply. In case of nutritional deficiency, there is potential depletion of thiamine stores within 2 weeks due to limited body stores and high turnover rate (half-life <10 days). Thiamine’s hydrosolubility and renal clearance profile make humans susceptible for TD throughout life.\[4\]

TD occurs predominantly in populations consuming polished rice and wheat flour (thiamine-deficient diet) and in those with poor consumption of meat, fish, and vegetables (sources of thiamine) and raw and fermented fish sauce (foods rich in thiaminase natural thiamine-degrading enzyme). Despite being easily treatable, TD has a significant morbidity and sequelae in all age groups, both in high- and low-resource countries. Decades of strong public health attention has made infantile TD (beriberi) very rare.\[5\]

The diagnosis of classic beriberi is still underreported, necessitating increased clinical awareness. Historically, the clinical features of TD have been categorized into three main types, namely, the pure cardiac form or wet TD, the aphonie form, and the neurologic or dry form. “Shoshin beriberi,” the more severe form, presents as cardiac failure and lactic acidosis.\[6\] TD having a wide varied clinical spectrum can mimic critical illness or polyneuropathies.\[7\] In pediatrics, the clinical diagnosis of TD is extremely frequently misdiagnosed, more so in resource-limited settings.\[4\]

The breast milk content of thiamine and its derivatives is around 0.21 mg/L. TD breast milk is common, exhibiting serious effects in exclusively breastfed infants.\[4\]

Postpartum TD has been found in Karen refugee mothers and breastfeeding Cambodian and Lao mothers. In addition, pregnant mothers in China were found thiamine deficient.\[5\] In these areas, TD was associated with a high infant mortality, which declined significantly after supplementation. TD has also been documented by developed nations in children requiring total parenteral nutrition mostly with deficient formulas in the PICU.\[4\]

The estimated daily recommended dietary allowance (RDA) of thiamine in children is 0.2 mg, 0.3 mg, and 0.6 mg up to 6 months of age, 7 months–3 years of age, and 4–8 years of age, respectively. Over 8 years, daily RDA varies from 0.9 mg to 1.2 mg.

Practical diagnostic definitions for TD are few. A study has defined possible TD in infants as acute symptoms in previously healthy breastfeeding infants associated with cardiac failure (tachypnea >50/min, tachycardia >170/min, gallop, and hepatomegaly >3 finger’s breadth) or loss of voice. Probable TD was defined if symptoms recovered after thiamine treatment.\[4\]

Thiamine pyrophosphate levels are a useful tool in investigating TD. They are measured using plasma, erythrocytes, and whole blood. Furthermore, urinary excretion of thiamine before and after exogenous thiamine administration is another method. In severe acute conditions, serum or whole-blood thiamine has a poor sensitivity and specificity as it decreases during systemic inflammation. It represents only a fraction of the whole-body thiamine pool. The standard is erythrocyte transketolase activity which accurately evaluates the thiamine status of the body. However, concerns do exist regarding the viability of the same in resource-limited settings and usefulness in acute conditions.

Considering the paucity of specific diagnostic tests, therapeutic thiamine challenge remains the only way to diagnose TD. Thiamine administered by slow IV injection over 30 min is safe. In severe acute conditions, rapid clinical improvement will be seen (within hours or days) following thiamine administration.
There is no conclusive evidence regarding pediatric thiamine dosage for severe acute illness. Rao and Chandak\(^\text{(8)}\) used 150 mg IV thiamine to treat breastfed infants under 6 months of age presenting with cardiac failure and/or tachyypnea, whereas Qureshi et al.\(^\text{(9)}\) successfully treated lactic acidosis in younger infants (aged 32 days to 4 months) with 100 mg of thiamine daily. Hubert Barennes et al.\(^\text{(10)}\) treated infants with suspected TD with Vitamin B1 tablets, 30 mg/day for 20 days, and those with acute symptomatic TD received an intramuscular (IM) or slow IV injection of thiamine (100 mg IM for mothers and 50 mg for infants). In view of paucity of evidence, some authors have continued lifelong thiamine supplementation.\(^\text{(7)}\) Hence, in children with severe acute conditions, early IV thiamine injection should be considered. It would not be an exaggeration to call thiamine a “complementary resuscitation tool.”

The present case presented a diagnostic challenge. First, the initial symptoms were predominantly respiratory, and cardiac involvement was limited only to pulmonary circulation. Second, the cardiac output was not hyperdynamic. Usually, beriberi is thought as a high-output failure, but cardiac output and ventricular filling pressure are extremely variable. The work of both ventricles is increased in TD, but that of the right rises more than that of the left. Third, the age of presentation was much later. Bhat et al.\(^\text{(10)}\) studied 29 exclusively breastfed infants having pulmonary hypertension, with their mean age at presentation being 78.45 ± 30.7 days. Our patient’s age was 7 months.

In summary, the present report revealed that TD can present with isolated pulmonary hypertension. TD being potentially fatal and readily treatable, empirical treatment with thiamine in cases of pulmonary hypertension of unknown cause merits early consideration. However, there is still no firm evidence for the best pediatric dosage and duration of therapy in severe TD.

**Learning points**

- As most pediatricians have low index of suspicion for TD, only a small fraction of cases of reversible pulmonary hypertension in infancy due to TD are diagnosed
- TD should be suspected in any cardiogenic shock not responding to appropriate therapy during infancy, worsening with diuretics
- Early thiamine injection in children with severe acute conditions should be considered as a “complementary resuscitation tool”
- Rapid point-of-care lactate testing demonstrating persistent lactic acidosis despite correction of shock raises the suspicion of TD.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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