

Thiamine-responsive acute pulmonary hypertension – A case series and review from a pediatric ICU



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ABSTRACT

Pulmonary hypertension is seen in approximately 10% of infants with respiratory distress admitting to pediatric ICUs. Causes can be idiopathic or secondary to lung parenchymal or vascular diseases. Among various causes of pulmonary arterial hypertension, thiamine deficiency (TD) is one of the reversible causes. TD is still prevalent in selected parts of India. This review outlines five typical patients admitted to KIMS, Amalapuram, with thiamine-responsive acute pulmonary hypertension who responded dramatically to thiamine supplementation. It can cause life-threatening pulmonary hypertension in exclusively breastfeeding infants of mothers who are on a restricted diet predominantly consisting of polished and washed rice which can contribute to infant mortality. Thiamine administration based on clinical suspicion and echo findings leads to remarkable recovery. To tackle this fatal disease, a very high degree of awareness and thiamine supplementation in relevant geographical areas is required.

Keywords: Thiamine; Cardiomegaly; Pulmonary hypertension; 2D ECHO

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INTRODUCTION

Pulmonary hypertension is seen in approximately 10% of infants with respiratory distress admitting to pediatric ICUs. Causes can be idiopathic or secondary to lung parenchymal or vascular diseases. Among various causes of pulmonary arterial hypertension (PAH), thiamine deficiency (TD) is one of the reversible causes.¹ Panigrahy et al., speculated two mechanisms for pulmonary hypertension in these infants with TD. Infants are particularly susceptible to TD in the initial months of life, and exclusively breastfed infants of thiamine-deficient but otherwise asymptomatic mothers are at the highest risk.² Infantile TD continues to be an important cause of mortality and long-term morbidity in

infants in developing countries.^{3,4} The first mechanism is that of pulmonary venous hypertension and the second mechanism is through the production of superoxide anions and other reactive oxygen species and reactive nitrogen species.⁴ A high index of suspicion for early identification of TD as a cause of pulmonary hypertension in early infancy and a low threshold for thiamine administration are keys to the optimal management of these critically ill infants.⁴ The present case series highlights reversible pulmonary hypertension as a potentially common but possibly underdiagnosed manifestation of TD.

This study describes the clinical profile and management outcome of five infants with severe pulmonary artery

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hypertension who were admitted in a tertiary care rural-based medical college hospital. After complete physical examination, routine laboratory investigations such as hemogram, chest X-ray, ABG with lactate, and 2D echo were done in all patients. In all cases, the diagnosis was based on echocardiogram evidence of pulmonary artery hypertension (dilated right atrium, right ventricle with bulging of the interventricular septum to the left with tricuspid regurgitation) and resolution after intravenously administration of thiamine. Intravenous thiamine (100 mg) was given as an infusion over 1 h, once a day for 3 consecutive days for all infants, followed by oral thiamine once a day for 3 months. Serial echocardiography was done at 8 h, 12 h, 24 h, and every day until discharge. Follow-up was done at 1 month and 3 months.

CASE 1

A 9-month-old female infant brought with complaints of respiratory distress and cyanosis. Antenatal events were uneventful, the baby was delivered at term, with a birth weight of 2.6 kg, vigorous at birth, with no NICU stay. Admission weight was 5.9 kg (<-3SD) and had normal development. At presentation, the baby had tachypnea, tachycardia, hypoxia (SpO₂ 92% in room air), and respiratory distress. The liver was palpable 5 cm below the right costal margin. This infant rapidly deteriorated with acidosis and hypoxemia, requiring conventional mechanical ventilation. Chest X-ray showing cardiomegaly with right atrium dilatation and prominent pulmonary trunk (Figure 1). Echocardiography showed marked right ventricular and right atrial with the interventricular septum deviated to the left ventricle with severe PAH (68 mm Hg) without any evidence of structural heart disease. Pulmonary hypertension, sudden onset with rapid progression of symptoms, and poor initial response to therapy in an exclusively breastfed baby prompted us to suspect “TD.” The thiamine concentration was 15.76 µg/L (reference range: 28.00–85.00 µg/L), and the mother’s thiamine level was 10 µg/L. Considering the probability of TD, intravenous thiamine was started. The baby showed clinical improvement, could be weaned off oxygen by 24 h, and respiratory distress subsided by 3 days. Repeat echocardiography at 24 h showed marked improvement with only mild PAH and subsequently showed complete resolution of PAH at 72 h. The infant needed an injection of adrenaline and an injection of milrinone for correction of shock and as vasodilators.

CASE 2

A 4-month-old male infant brought with complaints of fever with cough and cold for 5 days and increasing respiratory



Figure 1: Chest X-ray: Showing cardiomegaly with right atrium dilatation and prominent pulmonary trunk

distress. Antenatal events were uneventful, the baby was delivered at term, with a birth weight of 3 kg, vigorous at birth, with no NICU stay. Admission weight was 4.5 kg (<-3SD) and had normal development. At presentation, the baby had tachypnea, tachycardia, hypoxia (SpO₂ 88% in room air), and respiratory distress. The liver was palpable 3 cm below the right costal margin. Echocardiography showed features of severe PAH (60 mm Hg), without any evidence of structural heart disease. Pulmonary hypertension, sudden onset with rapid progression of symptoms, in an exclusively breastfed baby prompted us to suspect TD, but thiamine levels could not be sent due to financial constraints. Considering the probability of TD, intravenous thiamine was started. The baby showed clinical improvement, could be weaned off oxygen by 24 h, and respiratory distress subsided by 2 days. Repeat echocardiography at 24 h showed marked improvement with only mild PAH and subsequently showed complete resolution of PAH at 48 h. No pulmonary vasodilators other than oxygen were given.

CASE 3

A 2-month-old female infant brought with complaints of poor feeding, increased work of breathing with grunt, and cyanosis. Antenatal events were uneventful, the baby was delivered at term, with a birth weight of 2.8 kg, vigorous at birth, with no NICU stay. Admission weight was 3.9 kg (-3SD–-2SD) and had normal development. At presentation, examination revealed tachycardia, tachypnea, and bilateral crepitations. The liver was palpable 4 cm below the right costal margin. This infant rapidly deteriorated with marked lactic acidosis and hypoxemia, requiring conventional mechanical ventilation. Echocardiography showed marked right ventricular and right atrial with the interventricular septum deviated to the left ventricle with

severe PAH (54.3 mm Hg) (Figure 2) without any evidence of structural heart disease. Pulmonary hypertension, sudden onset with rapid progression of symptoms, and poor initial response to therapy in an exclusively breastfed baby prompted us to suspect “TD.” Pulmonary hypertension, sudden onset with rapid progression of symptoms, and poor initial response to therapy in an exclusively breastfed baby prompted us to suspect “TD.” The thiamine concentration was 3.5 µg/L (reference range: 28.00–85.00 µg/L), and the mother’s thiamine level was markedly low (5.5 µg/L). Considering the probability of TD, intravenous thiamine was started. The baby showed clinical improvement by 10 h, and respiratory distress subsided by 5 days. Repeat echocardiography at 10 h showed marked improvement with only mild PAH and subsequently showed complete resolution of PAH at 7 days. The infant needed an injection of adrenaline, an injection of milrinone, and an injection of noradrenaline for correction of shock.

CASE 4

A 7-month-old female infant brought with complaints of respiratory distress and reduced acceptance of feeds. Antenatal events were uneventful, the baby was delivered at term, with a birth weight of 3.2 kg, vigorous at birth, with no NICU stay. Admission weight was 5.8 kg (–3SD–2SD) and had normal development. At presentation, physical examination revealed tachycardia, tachypnea, and bilateral crepitations. The liver was palpable 5 cm below the right costal margin. This infant rapidly deteriorated with acidosis and hypoxemia, requiring conventional mechanical ventilation. Echocardiography showed marked right ventricular and right atrial with the interventricular septum deviated to the left ventricle with

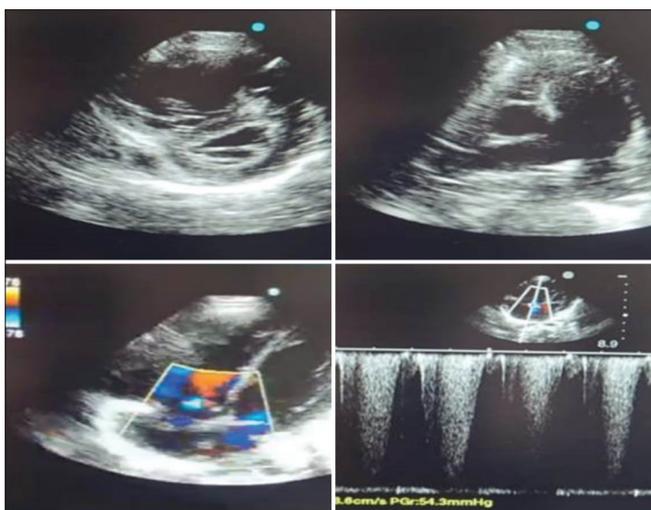


Figure 2: Echocardiogram: Showing septal flattening, dilated right atrium and main pulmonary trunk, tricuspid regurgitation, RVSP 54 mm Hg

severe PAH (65 mm Hg) without any evidence of structural heart disease. The thiamine concentration of the child was 10 µg/L (reference range: 28.00–85.00 µg/L), and the mother’s thiamine level was 28 µg/L. Considering the probability of TD, intravenous thiamine was started. The baby showed clinical improvement, and respiratory distress subsided by 3 days. Repeat echocardiography at 24 h showed marked improvement with only mild PAH and subsequently showed complete resolution of PAH at 7 days. The infant needed an injection of adrenaline, an injection of milrinone, an injection of noradrenaline for correction of shock, and tablet sildenafil as vasodilators.

CASE 5

A 1½-month-old female infant brought with complaints of cough, fast breathing, and irritability for the past 3 days. Antenatal events were uneventful, the baby was delivered at term, with a birth weight of 2.2 kg, vigorous at birth, with no NICU stay. Admission weight was 3.5 kg (–2SD–3SD) and had normal development. At presentation, the baby had tachypnea, tachycardia, hypoxia (SpO₂ 91% in room air), and respiratory distress. The liver was palpable 5 cm below the right costal margin. Other system examination of normal echocardiography showed features of severe PAH (52 mm Hg), without any evidence of structural heart disease. Pulmonary hypertension, sudden onset with rapid progression of symptoms, and poor initial response to therapy in an exclusively breastfed baby prompted us to suspect TD. The thiamine concentration was 11 µg/L (reference range: 28.00–85.00 µg/L), and the mother’s thiamine level was 25 µg/L. Considering the probability of TD, intravenous thiamine was started. The baby showed clinical improvement in 12 h and respiratory distress subsided by 2 days. Repeat echocardiography at 12 h showed marked improvement with only mild PAH and subsequently showed complete resolution of PAH at 48 h. No pulmonary vasodilators other than oxygen were given.

In all five cases, mothers were on a diet of polished and washed white rice. Infants were exclusively breastfed. These infants received an IV dose of thiamine (100 mg) over 1 h, followed by parenteral and then enteral supplementation with the resolution of symptoms. Repeat echocardiogram showed resolution of pulmonary hypertension and infants were healthy at follow-up. Both mother and infants received thiamine supplementation for 3 months (Table 1).

DISCUSSION

This study describes a small cohort of infants with right heart failure and severe pulmonary hypertension. They were all previously well, with normal growth. They presented with

Table 1: Results of all five cases of thiamine-responsive pulmonary artery hypertension

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5
Age	9 months	4 months	2 months	7 month	1.5 months
Gender	Female	Male	Female	Female	Female
Birth weight	2.6 kg	3 kg	2.8 kg	3.2 kg	2.2 kg
Current weight	5.9 kg (-3SD--2SD)	4.5 kg (<-3SD)	3.9 kg (<-2SD)	5.8 kg (-3SD--2SD)	3.5 kg (-2SD--1SD)
Chief complaints	Respiratory distress, cyanosis, shock	Increase respiratory distress, fever with cold decreased feed intake	Poor feeding, increased work of breathing, with grunt, cyanosis	Cough, fast breathing, irritability, shock	Cough, fast breathing, irritability
Examination findings	Tachycardia, tachypnea hepatomegaly	Tachycardia, tachypnea hepatomegaly	Tachycardia, tachypnea hepatomegaly	Tachycardia, tachypnea hepatomegaly	Tachycardia, tachypnea hepatomegaly
Maternal diet	Polished rice	Polished rice	Polished washed white rice	Polished washed white rice	Polished washed white rice
Infant diet	Exclusive breastfeeding and cereals-based complementary feeds	Exclusive breastfeeding	Exclusive breastfeeding	Exclusive breastfeeding	Exclusive breastfeeding
Right ventricular systolic pressure after thiamine infusion	68 mmhg	60 mmhg	54.3 mmhg	65mm Hg	52 mm Hg
Right ventricular systolic pressure after thiamine infusion	23 mmhg	21 mmhg	24 mmhg	22 mm hg	20 mm Hg
Respiratory support	Mechanical ventilation	HHHFNC	Mechanical ventilation	Mechanical ventilation	HHFNC
Pulmonary vasodilator	Injection milrinone, injection Epinephrine	-	Injection milrinone, injection Epinephrine, injection noradrenaline	Injection milrinone, injection Epinephrine, injection noradrenaline Tablet sildenafil	-
Thiamine levels in infants normal: 28.00–85.00 µg/L	15.76	-	3.5	10	11
Thiamine levels in mother normal: 28.00–85.00 µg/L	10	-	5.5	28	25
Response to thiamine administration	3 days	2 days	5 days	5 days	2 days
Resolution of PAH after thiamine administration	Improvement started by 24 h and resolution by 3 days	Improvement started by 24 h and resolution by 3 days	Improvement started by 10 h and resolution by 7 days	Improvement started by 3 days and resolution by 7 days	Improvement started by 12 h and resolution by 2 days

short duration of respiratory distress. The most common findings were tachycardia, tachypnea, and hepatomegaly. Severe pulmonary hypertension on echocardiography was a universal finding. Severe pulmonary hypertension can develop due to an increased pulmonary arterial blood flow and elevated LV end-diastolic pressure.⁵ There was no respiratory or cardiac etiology that could explain the clinical picture. The response to the thiamine administration was dramatic. The resolution of the disease was complete in 100% of the infants within 3–4 days.

In a study by Sastry et al., the mean age was around 3.2 months. The mean age of presentation in our study is 4.2 months. 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 significant morbidity and sequelae in all age groups, both in high- and low-resource countries. Decades of

strong public health attention have made infantile TD (beriberi) very rare.⁶

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 aphonic form, and the neurologic or dry form. “Shoshin beriberi,” the more severe form, presents as cardiac failure and lactic acidosis.⁷ In pediatrics, the clinical diagnosis of TD is extremely frequently misdiagnosed, more so in resource-limited settings.⁸

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. Post-partum TD has been found in Karen refugee mothers and breastfeeding Cambodian and Lao mothers. In addition, pregnant mothers in China were found thiamine deficient. In these areas, TD was associated with 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. Infantile TDD, the earliest manifestation of deficiency at 1ty, which declined significantly after supply-specific early signs such as refusal to breastfeed, irritability, vomiting, and persistent crying that is difficult to console.⁹

There is no conclusive evidence regarding pediatric thiamine dosage for severe acute illness.¹⁰ Rao and Chandak used 150 mg IV thiamine to treat breastfed infants under 6 months of age presenting with cardiac failure and/or tachypnea, whereas Qureshi et al.,¹¹ successfully treated lactic acidosis in younger infants (aged 32 days to 4 months) with 100 mg of thiamine daily. Barennes et al., 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 the paucity of evidence, some authors have continued lifelong thiamine supplementation.¹² Bhat et al.,⁵ studied 29 exclusively breastfed infants having pulmonary hypertension, with their mean age at presentation being 78.45±30.7 days, Quereshi et al., mean age was 78.25 days and hence, in children with severe acute conditions, early IV thiamine injection should be considered. In summary, the present case series highlights 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.

CONCLUSION

In a previously well exclusively breastfeeding infant, thiamine-responsive acute pulmonary hypertension can present as acute onset of respiratory distress. Tachycardia, tachypnea, and hepatomegaly are very consistent signs and symptoms. Echocardiography shows evidence of severe pulmonary hypertension. Administration of thiamine leads to rapid improvement within hours and delayed treatment can be fatal. The important contributing factors are diet and cultural practices. A very high level of clinical suspicion is required to recognize this easily treatable but fatal disease.

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