



## Original Article

## Shoshin beriberi–thiamine responsive pulmonary hypertension in exclusively breastfed infants: A study from northern India



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## ABSTRACT

**Objective:** To study the effect of thiamine administration on the resolution of pulmonary hypertension in exclusively breastfed infants.

**Design:** Prospective cohort study.

**Setting:** Hospital based study of a tertiary care hospital.

**Patients:** A total of 29 infants with 17 males (58.6%) and 12 females (41.4%) were included in the study.

**Intervention:** In addition to the management of shock, right heart failure and renal failure, patients received intravenous thiamine 100 mg/kg IV followed by 10 mg/day till introduction of supplementary feeds.

**Main outcomes measures:** Resolution of shock, metabolic complications and pulmonary hypertension.

**Results:** Mean age at presentation was  $78.45 \pm 30.7$  days. All infants were exclusively breastfed. 86.2% of mothers were on customary dietary restrictions. Biventricular failure and tachycardia was commonly present. There were four deaths in our series. Acute metabolic acidosis was a universal feature with a mean pH of  $7.21 \pm 0.15$ . Pulmonary hypertension was present in all patients on admission. Intravenous thiamine 100 mg/kg IV was given immediately after documenting pulmonary hypertension. Repeat echocardiography showed complete resolution of pulmonary hypertension.

**Conclusion:** Many infants present to us with Shoshin beriberi with unusually high pulmonary pressures. These patients respond to thiamine challenge with prompt resolution of metabolic complications and reversal of pulmonary hypertension. We believe this is first of its kind from the region, which is reported.

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## 1. Introduction

Kashmir, a northern state of India, is in the middle of an infantile beriberi epidemic,<sup>1,2</sup> due to high consumption of polished rice. Traditionally, here rice is washed multiple times before cooking, which further depletes the thiamine content. The requirement already high during fever, pregnancy, and lactation is further

increased when carbohydrates like rice are taken in large quantities.<sup>3</sup> Lactating women in this part of the world are more prone to thiamine deficiency due to traditional food avoidance practices and taboos in the postpartum period, wherein they consume diet comprising predominantly of rice with meat or chicken soup. Epidemics of infantile beriberi are known to occur among exclusively breastfed infants of thiamine deficient mothers.<sup>4</sup>

The onset of symptoms is often very rapid and the fatality rate is high. It can present in different forms like pure cardiovascular, aphonic and pseudomeningitic.<sup>3</sup> Cardiovascular beriberi is typically accompanied by high cardiac output, decreased systemic blood pressure and tachycardia. “Shoshin beriberi” is a fulminant form of cardiovascular beriberi. It has been appropriately designated as “a rapidly curable hemodynamic disaster” with an

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extremely high mortality if not treated early.<sup>5</sup> It is characterized by hypotension, tachycardia, and lactic acidosis.<sup>6–8</sup> Severe pulmonary hypertension can develop due to an increased pulmonary arterial blood flow and elevated LV end-diastolic pressure.<sup>9</sup> This form of beriberi promptly responds to rapid intravascular administration of thiamine, which improves the adverse hemodynamic situation within minutes, in fact, this is diagnostic of this rare condition.<sup>7–9</sup> Shoshin beriberi has been most commonly seen in adult men and pregnant women and is extremely rare in infants.<sup>3</sup>

We have been admitting a number of exclusively breast fed infants in our intensive care unit, with sudden onset of unexplained bi-ventricular failure, respiratory distress, severe pulmonary hypertension and acute lactic acidosis. Given the high endemicity of infantile thiamine deficiency in this region, typical constellation of signs and symptoms of Shoshin beriberi and nonspecific lactic acidemia, thiamine was instituted as a first-line treatment in these infants. The response to thiamine was quick and there was a dramatic improvement in pulmonary hypertension. The purpose of this study was to describe this rare fulminant form of infantile thiamine deficiency presenting as pulmonary hypertension in a large series of infants.

## 2. Materials and methods

This study was a prospective hospital-based study conducted in the Department of Pediatrics, Sher-I-Kashmir Institute of Medical Sciences Srinagar, a tertiary care hospital in northern India, from January 2014 to September 2015. Ethical clearance was sought from the hospital ethical board. Written informed consent was taken from the parents/caregivers of the study subjects.

Eligibility criteria were exclusively breastfed infants between 1 and 6 months of age who presented with acute onset pulmonary artery hypertension (PAH). Although cardiac catheterization is a gold standard to diagnose PAH, echocardiography is the most useful noninvasive tool that is used to detect PAH.<sup>10</sup> We used conventional two-dimensional (2D) echocardiography to diagnose PAH in our patients, as it was readily available in our pediatric intensive care unit (PICU) and could provide a qualitative and quantitative evaluation of the severity of PAH.<sup>10</sup> PAH was defined as Doppler-estimated pulmonary arterial systolic pressure of  $\geq 40$  mm Hg. Cardiac beriberi with PAH was said to be present if infants had all of the following: (1) an enlarged heart with normal sinus rhythm and elevated venous pressure with or without shock, (2) metabolic acidosis on arterial blood gas (ABG) analysis, (3) no other evident cause, (4) prompt response to thiamine.<sup>11</sup> Thiamine levels could be determined in two infants only due to financial constraints.

All patients were evaluated as per unit protocol, which included 2D echocardiography, chest radiograph, arterial blood gases, blood sugar, electrolytes, alanine transaminase, urea, creatinine, serum lactate and complete blood counts, blood culture, cerebrospinal fluid analysis, tandem mass spectrometry (TMS) and urine gas chromatography–mass spectrometry (GC–MS).

Exclusion criteria included any congenital heart disease, inborn error of metabolism, blood culture confirmed sepsis, any known chronic systemic disease.

Baseline demographic, clinical data were collected from all the study subjects, which included dietary history in the mother, social economic status using Kuppaswamy's Socio-economic Status Scale, age, birth order, consanguinity, type of feeds given, any previous systemic disease, family history of pulmonary hypertension, anthropometry, and vital parameters.

### 2.1. Statistical analysis

Data were entered in Microsoft Excel 2007. Normality of data was checked by the Shapiro–Wilk test and by checking kurtosis

and skewness. Parametric data are presented as mean  $\pm$  SD, nonparametric data as median (IQR). The Wilcoxon signed-rank test was used to observe the intragroup difference in PAH before and after thiamine administration.

## 3. Results

A total of 29 infants were enrolled in the study with 17 males (58.6%) and 12 females (41.4%). Mean age at presentation was  $78.45 \pm 30.7$  days. All infants were exclusively breastfed. 86.2% of mothers were on dietary restrictions guided by local customs. The majority of infants were from poor families; 15 belonging to the lower socioeconomic class and eight to the upper-lower socioeconomic class. Consanguinity was reported in twelve (41.4%) infants. The mean weight of the study population was  $5 \pm 1$  kg and it was appropriate for age in all infants.

Table 1 shows the clinical features of the study population. Right heart failure was a universal finding. Biventricular failure was seen in 75% of patients; it was more common in infants who had symptoms for more than 12 h. Tachycardia was a common finding, with a mean heart rate of  $160 \pm 26$  beats per minute (BPM). Fourteen (48%) infants presented with oliguria, which improved after fluid resuscitation in ten. However, four infants developed complete renal shutdown. Transient transaminitis was a common finding; visible jaundice was noticed in three. Symptoms followed a febrile episode in nine (31%) infants. There was temporal relation with vaccination in four (13%) infants, with symptoms following pentavalent (DPT, Hib, Hep B) vaccination. There were four deaths in our series; all these infants had presented with irreversible shock and renal failure.

Table 2 presents baseline laboratory features of the studied group. Acute metabolic acidosis was a universal feature with a mean pH of  $7.21 \pm 0.15$ . Serum lactate was elevated in 27 patients with median lactate (IQR) of 4.1 (6.6). Twenty-seven blood cultures were sterile. Two cultures showed positive growth for coagulase negative *Staphylococcus aureus* (CONS) possibly due to contamination. Blood lactate was elevated in majority. Blood thiamine diphosphate (TDP) levels were 19 and 24 nmol/l (normal  $>80$  nmol/l) in two infants. The median (IQR) pulmonary artery pressure was 48 (11) mm of Hg.

The majority of infants presented with shock, which was managed with normal saline boluses, dopamine and adrenaline

**Table 1**  
Clinical features of the study population.

Clinical features	N (%)
CVS	
Tachycardia	25 (86.2)
Shock	22 (75.86)
Central cyanosis	12 (41.3)
Cardiomegaly	20 (68.9)
Dependent edema	19 (65.5)
TR murmur	27 (93)
Respiratory	
Tachypnea	20 (68.9)
Gaspings breathing	5 (17.2)
CNS	
Irritability	24 (82.7)
Vacant stare	4 (13.7)
Renal	
Oliguria	14 (48.2)
Hepatobiliary	
Hepatomegaly	29 (100)
Visible jaundice	3 (10)
Fever	9 (31)

**Table 2**  
Baseline laboratory data of study participants.

Parameter	Value
pH (mean ± SD)	7.21 ± 0.15
HCO <sub>3</sub> (mean ± SD)	11.5 ± 5.18
Lactate (median (IQR))	4.1 (6.6)
pCO <sub>2</sub> (mean ± SD)	28.34 ± 7.32
Total leukocyte count (median (IQR))	15,600 (8665)
Hemoglobin (mean ± SD)	12.9 ± 2
Blood urea (median (IQR))	39 (25)
Serum creatinine (median (IQR))	0.9 (0.55)
Serum aspartate amino transferase	46 (71)
Serum sodium (mean ± SD)	138 ± 7.2
Serum potassium (mean ± SD)	4.5 ± 0.76
Negative blood cultures (%)	27 (93)
Positive C reactive protein (%)	5(17)

infusion as per unit protocol. Mechanical ventilation was needed in 12 infants; the median (IQR) duration of ventilation was eight (9.25) hours. Intravenous antibiotics were started in 24 infants on an empiric basis, which were later discontinued after blood cultures showed no growth. Intravenous thiamine at a dose of 100 mg/kg was given after documenting pulmonary hypertension. Later oral thiamine was started at 10 mg/day which was continued till complementary feeds were started. Four infants needed peritoneal dialysis for complete renal shutdown.

Repeat echocardiography done after 4–6 weeks showed complete resolution of pulmonary hypertension in 25 infants, with a median (IQR) pulmonary pressure of 25 (12) mm of Hg. There was a statistically significant drop in pulmonary hypertension (<0.05).

#### 4. Discussion

With the advent of mechanical rice milling in the late 19th century, beriberi became a dominant public health problem in Asia, responsible for considerable mortality, especially amongst infants.<sup>12,13</sup> The majority of the rice eating countries have conquered this disease due to strong public health attention. Nevertheless, Kashmir is still gripped by thiamine deficiency epidemic,<sup>1,2</sup> due to high consumption of thoroughly washed milled rice and other dietary taboos during the postpartum period. Barennes et al., in a survey of 22 thiamine deficient villages of North Laos found similar practices prevalent among mothers.<sup>14</sup> Qureshi et al.<sup>1</sup> has reported a case series of thiamine responsive acute life-threatening metabolic acidosis in exclusively breastfed infants from this region.

Pulmonary hypertension in cardiac beriberi is rare. It occurs as a result of progressive vasodilatation and/or damage to the myocardium that leads to circulatory breakdown and increased left ventricular end diastolic pressure. Direct impairment of myocardial energy production has been proposed as one possible mechanism as thiamine is required as a cofactor for energy production.<sup>15</sup> In addition to falling systemic blood pressure and shock the clinical picture includes vasoconstriction in skin and kidney, which will provoke cyanosis and acute renal shutdown. This extreme form of cardiac beriberi also known as Shoshin beriberi is not common. Recently some cases in adults have been reported from East Asia and some developed countries.<sup>6,9</sup> It is extremely rare in infants. We report a large series of exclusively breastfed infants with Shoshin beriberi and pulmonary hypertension, which is of the first kind reported from this region. Patients were diagnosed on the basis of modified predefined diagnostic criteria<sup>11</sup> which included response to thiamine administration. The acute symptoms were immediately corrected, pulmonary hypertension resolved completely within 4–6 weeks.

Response to thiamine is a gold standard for diagnosis of beriberi especially Shoshin beriberi.<sup>3,7–9</sup> A standard laboratory diagnosis of thiamine deficiency is made by assessing the erythrocyte transketolase activity at baseline and after the administration of thiamine.<sup>16</sup> This test, however, is non-specific or inconclusive and rarely performed in clinical practice.<sup>17</sup> In our series thiamine challenge reversed both metabolic abnormalities and cardiovascular manifestations completely. Thiamine diphosphate (TDP) levels were done in two infants, which were grossly low thus further confirming our results.

Pulmonary hypertension in this age group is common as a consequence of congenital heart disease. We excluded infants with congenital heart disease. Similarly, there was no prior history of persistent pulmonary hypertension of newborn (PPHN) in our series.

We used 2-dimensional echocardiography for the diagnosis of pulmonary hypertension, as this is the most useful imaging modality for diagnosis of pulmonary hypertension. It is handy and can be performed in the emergency situation. Also, it can evaluate pulmonary hypertension quantitatively and precisely.<sup>10</sup> Pulmonary hypertension is suspected on finding dilatation of the right ventricle and flattening of the interventricular septum with a D-shaped deformation of the left ventricle. Tricuspid valve regurgitation is also indirect evidence. When measured directly in the cardiac catheterization laboratory, the normal pulmonary artery (PA) systolic pressure of children is ≤30 mm Hg and the mean PA pressure is ≤25 mm Hg at sea level. The estimated upper 95% limit for PA systolic pressure by Doppler ultrasound is 37.2 mm Hg. (This results from a tricuspid regurgitation jet velocity of 2.7 m/s in the absence of pulmonary stenosis.) Thus, a Doppler-estimated PA systolic pressure of ≥40 mm Hg has been assumed as a cutoff value for PA hypertension in our patients.<sup>18</sup> The only drawback of echocardiography is that it overestimates pulmonary hypertension.

#### 5. Conclusion

To conclude, we are witnessing high incidence of infantile beriberi in this region, because of consumption of thoroughly washed milled rice and dietary taboos in the postpartum period. Many infants present to us with a fulminant form of wet beriberi known as Shoshin beriberi with unusually high pulmonary pressures on 2D echocardiography. These patients respond to thiamine challenge with prompt resolution of metabolic complications and reversal of pulmonary hypertension within few weeks of thiamine administration.

##### What is known about this article?

- Thiamine deficiency is known in exclusively breastfed babies of thiamine deficient mothers.

##### What this study adds

- Pulmonary hypertension can be the presenting feature of thiamine deficiency in exclusively breastfed babies, which responds to thiamine administration.

#### Conflicts of interest

The authors have none to declare.

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