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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 ± 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 ± 0.15. Pulmonary hypertension was present in all patients on admission. Intravenous thiamine 100 mg/kg IV stat 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.

1. Introduction

Kashmir, a northern state of India, is in the middle of an infantile beriberi epidemic,[1,2] 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 amounts.[3] 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.[4]

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.[3] 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.[5] It is characterized by hypotension, tachycardia, and lactic acidosis.[6–8] Severe pulmonary hypertension can develop due to an increased pulmonary arterial blood flow and elevated LV end-diastolic pressure.[9] 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.[7–9] Shoshin beriberi has been most commonly seen in adult men and pregnant women and is extremely rare in infants.[3]

We had been admitting a number of exclusively breastfed 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 academia, 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.[10] 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.[10] 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.[11] 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 Kuppuswamy'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	
Tacypnea	20 (68.9)
Gasping breathing	5 (17.2)
CNS	
Irritability	24 (82.7)
Vacant stare	4 (13.7)
Renal	
Oligurea	14 (48.2)
Hepatobiliary	
Hepatomegaly	29 (100)
Visible jaundice	3 (10)
Fever	9 (31)

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