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Case Series

Clinical spectrum of infants with thiamine responsive pulmonary arterial hypertension

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a progressive disorder caused by hypertension in blood vessels from heart to lungs. Exclusively breastfed infants are at the highest risk due to their high metabolic demand and low thiamine level in mothers. Symptoms are observed to be sometimes precipitated with the presence of co morbidity such as sepsis and lower respiratory tract infections. This study explains 10 cases with varied clinical presentation and response to management of different grades of infantile pulmonary arterial hypertension.

Keywords: Pulmonary arterial hypertension, Infancy, Thiamine

INTRODUCTION

Pulmonary hypertension (PH) in pediatric age group is most commonly associated with cardiac and respiratory diseases. Also, other causes such as various hematologic, hepatic, metabolic, oncologic, genetic, and rheumatologic disorders are described in the literature.[1] Although rare, association of Infantile PH in the setting of vitamin deficiencies (vitamin D, thiamine, and vitamin C) is exceedingly rare, but are reported.[2-4] Early infancy has traditionally been an uncommon age for presentation of new-onset PH. However, recently, numerous cases of severe PH due to thiamine deficiency were reported during early infancy from India. Here we review the spectrum of clinical presentation, hospital course, treatment options and outcome of 10 cases of thiamine-responsive acute pulmonary hypertension of early infancy. Pulmonary hypertension is defined as a mean pulmonary arterial pressure (mPAP) greater than 20 mm Hg at rest as per the sixth world symposium on pulmonary hypertension in 2018, and greater than 25 mm Hg at rest as per the guidelines issued by the European society of cardiology (ESC)/European respiratory society (ERS) in 2015. Recent guidance has suggested that echocardiographic assessment of pulmonary hypertension should be limited to determining the probability of pulmonary hypertension being present rather than estimating the pulmonary artery pressure. In patients for whom presence of pulmonary hypertension requires confirmation, it should be done with right heart catheterization when indicated.[5]

Table 1: 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension.

Grade	MPAP (mmHg)
Mild	25-40
Moderate	41-55
Severe	>55

CASE SERIES

Prospective observational study of infants presenting with various grades of PAH. Detailed history taking, clinical examination, basic investigations and echocardiography were performed. Dietary patterns of mothers were recorded. Thiamine was administered and serial echocardiography was performed to evaluate the response to treatment.

Table 2: Cases and details.

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age (months)	3	2	4	3	3	4	2	5	1.5	2
Gender	Male	Female	Male	Male	Male	Male	Male	Male	Female	Female
Current weight (in kg)	5.3	3.8	5.7	5	6.9	4.8	4.5	5.65	4.5	5.2
Birth weight (in kg)	2.9	2.5	3.5	2.6	3.67	2.5	2.5	2.8	2.5	4.2
Presenting symptoms and signs	Poor feeding, reduced urine output, hurried breathing, chest retractions	Poor feeding, un-responsive	Cough, change in voice, fever, chest retractions, bilateral lung crepitations	Difficulty in feeding, lethargy, regurgitation of feeds, hurried breathing	Crying and staining while passing stools, forehead sweating and suck rest suck cycles during feeding, tachypnea	Excessive crying, regurgitation of feeds	Cold, cough, hurried breathing, refusal of feeds, chest retractions	Noisy breathing, regurgitation of feeds, hurried breathing, change invoice	Noisy breathing, change in voice, regurgitation of feeds, inspiratory strider, tachycardia	Noisy breathing, hurried breathing, regurgitation of feeds
Family history of similar illness	-	-	-	-	Sibling- sudden death at 1.5 months of age	-	-	-	-	Sibling- sudden death at 3 months of age
Parental consangui-nity	Non-consanguin-eous	2 * consanguin e-eous marriage	Non-consanguin-eous	3 * consanguine-eous marriage	3 * consanguine-eous marriage	Non-consanguin -eous	Non-consanguine -ous	3 * consanguine -ous marriage	Non-consanguin-eous	Non-consanguin-eous
Hepatome-galy	-	-	-	-	Liver palpable 1.5 cm below right costal margin with liver span of 6.3 cm	-	-	-	-	Liver palpable 4 cm below right costal margin with liver span of 7 cm
Maternal diet	Polished, washed white rice	Polished, washed white rice	Polished, washed white rice	Polished, washed white rice	Polished, washed white rice	Polished, washed white rice	Polished, washed white rice	Polished, washed white rice	Polished, washed white rice	Polished, washed white rice

Continued.

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Infant diet	Exclusive breast feeds	Exclusive breast feeds	Exclusive breast feeds	Exclusive breast feeds	Exclusive breast feeds	Exclusive breast feeds	Exclusive breast feeds	Exclusive breast feeds	Exclusive breast feeds	Exclusive breast feeds
SPO_2 at admission (room air)	68%	40%	75%	50%	85%	95%	90%	85%	80%	50%
Respiratory support	Nasal prongs	Ventilator	HFNC	HFNC	Nasal prongs	-	Nasal prongs	Nasal prongs	Nasal prongs	Ventilator
Circulatory support	-	Fluid boluses, ionotropes	-	-	-	-	-	-	-	Fluid boluses, ionotropes
Time taken to wean to room air	2d	Death	4d	5d	3d	Maintained on room air	2d	3d	2d	5d
2D echo findings at admission	Pasp 68 mmHg, RA, RV dilated, PA and IVC dilated	Pasp 150 mmHg, with TAPVC	Pasp 66 mmHg, RA, RV dilated, PA and IVC dilated	Pasp 48 mmHg, RA, RV dilated.	Pasp 42 mmHg, RA, RV dilated	Pasp 42mmhg, RA, RV dilated	Pasp 42mmhg, RA, RV dilated, small ASD mm with left to right shunt	Pasp 40 mmHg	Pasp 76 mmHg, severe TR	Pasp 69 mmHg, dilated RA, RV trivial aortic and mitral regurgitation
Repeat 2D echo findings after 24-48 hours	32 mmHg	-	38 mmHg	30 mmHg	34 mmHg	15 mmHg	15 mmHg	30 mmHg	38 mmHg	51 mmHg
Treatment given	Thiamine, sildenafyl	Thiamine, sildenafyl	Thiamine, sildenafyl	Thiamine	Thiamine	Thiamine	Thiamine	Thiamine	Thiamine	Thiamine
Outcome	Satisfactory	Death	Satisfactory	Satisfactory	Satisfactory	Satisfacto-ry	Satisfactory	Satisfactory	Satisfactory	Satisfactory

Inclusion criteria

Infants presenting with mild, moderate, and severe PAH were included.

Exclusion criteria

Infants with significant lung disease, heart disease, sepsis, and inborn errors of metabolism were excluded.

Details of 10 cases are listed in Table 2.

5 out of 10 infants presented with severe PAH, 4 with moderate PAH and 1 with mild PAH. There has been 1 death out of 5 infants with severe PAH. All these infants received an IV dose of thiamine (100 mg) over 30 min followed by parenteral and then enteral supplementation with resolution of symptoms (Table 2). Repeat echocardiogram showed resolution of PH and infants were healthy at follow-up. Mothers received dietary recommendations and oral thiamine supplementation. The metabolic screen for inborn errors of metabolism was negative in all cases. The second case is of a 2month old infant with lethargy, gasping and cyanosis. This infant rapidly deteriorated with acidosis and hypoxemia, requiring conventional mechanical ventilation with pulmonary vasodilator and inotropic support. Over the next few hours, the infant deteriorated further with increasing respiratory distress and hypoxemia causing cardio respiratory arrest and death.

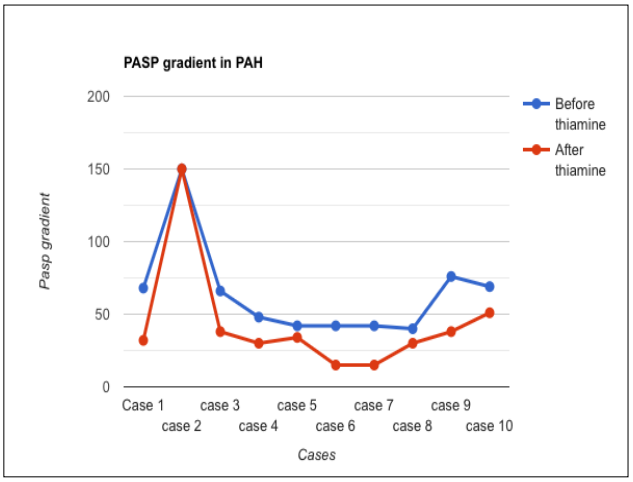

Figure 1: Line graph- response to thiamine therapy.

The clinical presentation in our patients was typical of PH exacerbated by a respiratory illness in previously healthy infants on exclusive breast feeding (Tables 2 and 3). These patients had severe respiratory distress, refractory hypoxemia, PH and lactic acidosis with some requiring mechanical ventilation, pulmonary vasodilators and inotropic support. These infants had a typical history of maternal customary dietary restriction and consumption of exclusive repeatedly washed and polished white rice and wheat flour (Table 2).

Thiamine requirement is greater in infants due to their relatively high metabolic rates.[10] Differential diagnosis of thiamine deficiency in infants include sepsis, meningoencephalitis, cardiomyopathy, complicated falciparum malaria, infantile kwashiorkor, metabolic encephalopathy and idiopathic pulmonary arterial hypertension.

Infants rapidly responded to IV thiamine 100 mg over 20–30 min and showed clinical improvement over the next 2–4 hours (Table 3 and Figure 1). All infants received enteral thiamine for a few weeks. After 24–48 hour of thiamine, significant improvement in PH was observed in these infants. Although, sildenafil was used in the management of these patients, these medications did not result in any significant change in clinical outcomes. Follow-up after 4 to 6 weeks of thiamine therapy showed complete resolution of this form of post-neonatal pulmonary hypertension.

Table 3: Demographic details and clinical profile of cases with PAH.

Clinical spectrum	Mean±SD (range)/ %
Gender ratio (male: female)	2.3:1
Age in months	2.95±1.1 (1.85-4.05)
Weight in kg	5.1±0.84 (4.26-5.94)
Weight centile	26.5±34 (7.5-60.5)
Duration for O_2 requirement	2.7±1.6 (1.1-4.3)
Clinical features	
Hurried breathing	60
Regurgitation of feeds	60
Feeding issues (poor feeding/ difficulty feeding)	50
Noisy breathing	40
Chest retractions	30
Cough	20
Excessive crying	20
Unresponsiveness	10
Echocardiographic features	
Pulmonary artery systolic pressure at admission	64.3±33.1 (31.2-97.4)
Pulmonary artery systolic pressure 24-48 hours after thiamine administration	43.3±38.9 (4.4-82.2)
Fall in PASP after thiamine administration	21±5.8 (15.2-26.8)

DISCUSSION

A recent estimation of the prevalence of the population at risk of dietary thiamine deficiency in India (based on national food balance sheets) was 14.8%.[11]

There is a rapid increase in the recognition of infants with PH in India those are responding to thiamine.[7]

PH due to malnutrition is likely a rare finding, but instances of vitamin D3, vitamin C and thiamine (B1) deficiency causing PH have been observed across different age groups. Recently several cases of infantile pulmonary hypertension are reported from India presenting in postneonatal age group.

Table 4. Age distribution of PAH cases.

Age (in months)	Number of infants	%
1-2	1	10
2-3	3	30
3-4	3	30
4-5	3	30
Total	10	100

The cases presented in our study were between 1-5 months of age (Table 4). 90% of them being after 2 months. In a recent case series published by Panigrahy et al.[6] Infantile thiamine deficiency related symptoms most commonly occur between 1 and 7 months of age. Risk factors for TRAPHEI include exclusive breastfeeding by thiamine-deficient but otherwise asymptomatic mothers. Mothers who consume exclusive polished white rice that has been washed multiple times are at the highest risk of thiamine deficiency. Young infants (1–3 months of age) exclusively breastfed are at greatest risk for developing thiamine deficiency.

Our case series we studied 10 infants with a mean postnatal age of 2.95 months (approx. 88.5 days) (Table 3).

Bhat et al studied 29 infants with a mean postnatal age of 78.45 days, who presented with clinical signs of acute onset PH.[12] All the babies included were exclusively breastfed and are from middle and lower socio-economic class families. Right heart failure and acute metabolic acidosis were universal findings.

Table 5: Gender distribution of PAH cases.

Gender	Number	%
Male	7	70
Female	3	30
Total	10	100

A case series by Narsimha et al described 55 infants with mean age of 3.9 months with clinical features of high-output cardiac failure with PH. Mean duration of illness was 7.5 days but data regarding severity of illness and need for ventilation were not provided. All these infants and their mothers belonged to low socio-economic groups and were thiamine-deficient based on low levels of ETKA. These infants showed a rapid response to thiamine confirming the diagnosis of cardiac beriberi. Nineteen babies were followed up after 2–3 weeks and demonstrated the resolution of PH with a reversal of echocardiographic abnormalities.

In our case series, 7 out of 10 cases (70%) presented are males and only 3 out of 10 (30%) are females (Table 5). A review of literature of cases of infantile PH from India (Sastry et al, Sangeeta et al, Kotyal et al) show that 65–70% of infants reported to date are male infants.[7-9] It is not clear if gender plays a role in the pathogenesis of PH. We cannot rule out societal preference to seek care for male infants. In addition, in some of these cases, there is past history of a sibling suffering from a similar illness often resulting in death. Familial recurrence could suggest the persistence of thiamine deficiency in the mother from pregnancy to pregnancy. A genetic component increasing susceptibility to low thiamine levels cannot be ruled out.

Barennes et al treated infants with acute symptomatic thiamine deficiency with an intramuscular (IM) or slow IV injection of 50 mg thiamine.[16-18] All infants with pulmonary hypertension completely resolved at 4 weeks of follow-up and no recurrence was observed at 6 months of follow-up.

The body's requirements depend exclusively on dietary supply as there is no endogenous thiamine synthesis in human body. If it not continuously replaced, stores of thiamine is depleted within 2 weeks due to the combination of limited body storage and a high turnover rate (half-life <10 days). Polished rice is the major dietary component (staple food) in some states of South India including Karnataka. Rich sources of thiamine are outer layer of cereals, legumes, pulses, potato, lean meat, milk and nuts.1 The process of milling, repeatedly washing, cooking rice in large amounts of water followed by discarding the excess water reduces the vitamin content.1 The diet in the postpartum period is mostly determined by cultural beliefs and taboos. Consumption of polished rice, lack of dietary diversity and food taboos are the factors that contribute to thiamine deficiency.[16,20,21]

Exclusively breastfed infants along with their high metabolic demand and also low thiamine level in mothers are at the highest risk. Symptoms are observed to be sometimes precipitated with the presence of co morbidity such as sepsis.

Table 6: Response to thiamine administration.

Pasp gradient on 2D echo (mmhg)	At admission	24-48 hrs after thiamine administration
Mean	64.3	31.4
Median	57	32
Mode	42	38

Echocardiogram can demonstrate PH. There is no demonstrable pulmonary or cardiac cause of PH by chest X-ray or echocardiogram. Clinical clues can lead to diagnosis. Lactic acidosis can suggest the possibility of

Thiamine responsive PAH. Thiamine must be administered empirically or prophylactically to such infants. Laboratory diagnosis of thiamine deficiency is fraught with many issues. Estimation of serum thiamine reflects recent intake and doe not reflect functional levels. Low erythrocyte transketolase activity (ETKA) and high thiamine-pyrophosphate effect (TPPE) can suggest functional thiamine deficiency which are expensive and not routinely available.[13-15] After initiation of treatment with thiamine A 25% increase in ETKA activity (TPPE effect) suggests severe deficiency. Response to thiamine administration with resolution of PH is observed to be diagnostic.[3,12,13] High degree of awareness among paediatricians is required for timely recognition and treatment.

Limitations

Laboratory testing for thiamine levels as an objective proof of deficiency was not possible due to financial and time constraints.

Lack of cardiac catheterisation, although a potential limitation, if performed would have delayed lifesaving treatment in babies with heart failure. Echocardiogram unequivocally showed severe PH.

CONCLUSION

Thiamine deficiency is a life threatening condition which is still prevalent in certain parts of India in exclusively breastfed infants with mother's diet predominantly consisting of polished rice. A high index of suspicion for early identification of thiamine deficiency as a cause of PAH in early infancy and a low threshold for thiamine administration are keys to the optimal management of these critically ill infants and to reducing their morbidity and mortality. The cases described here highlight a potentially critical but reversible manifestation of thiamine deficiency. In the absence of specific diagnostic tests in resource-limited settings, a low threshold for a therapeutic thiamine challenge is an easier way to diagnose thiamine deficiency. Awareness programs are required to educate Pediatricians, Anganwadi workers and other community health providers to aid in early recognition of the condition and prompt treatment to reduce morbidity and mortality. Government aids and policies should to fortify rice, salt, wheat and cereals with thiamine should be encouraged to assist in prevention. Furthermore, research and studies are required to provide insights on pathophysiology, diagnostic tests and management of thiamine deficiency in early infancy.

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