

Case Series

Thiamine responsive pulmonary hypertension: case series

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ABSTRACT

Pulmonary hypertension (PH) is most commonly related either to a cardiac or a pulmonary cause. But less commonly various hematological, hepatic, genetic causes are also associated. Infantile PH due to vitamin deficiencies is very rare though few cases with thiamine deficiencies causing PH have been reported lately. Lack of awareness and late recognition of thiamine deficiency may result in high mortality. A high index of suspicion is required for early diagnosis and management to decrease the severity and morbidity and thereby preventing long term implications on neurological development. Here, we described three cases of infants admitted to Kamineni academy of medical sciences diagnosed with PH who responded dramatically to thiamine supplements. The lack of rapid diagnostic capacity and the severe outcome of thiamine deficiency justify the use of a therapeutic thiamine challenge in cases with high clinical suspicion. Increased awareness about thiamine deficiency and low threshold for thiamine use should guide clinicians in their practice.

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

INTRODUCTION

Infantile PH due to vitamin deficiencies is very rare though few cases with thiamine deficiencies causing PH have been reported lately. Thiamine being an essential water soluble B1 vitamin needs to be supplied exogenously with limited body stores and high turnover rate.^{1,2} Thiamine diphosphate (TDP) is the predominant intracellular metabolite. TDP levels provide a better measure of body thiamine status but do not assess thiamine metabolic function. Erythrocyte transketolase activity (ETKA) is more accurate in assessing the functional thiamine status of the body. Thiamine is a co factor in many enzymatic processes like pyruvate to acetyl CoA by pyruvate dehydrogenase (lactic acidosis) ; alpha ketoglutarate to succinyl CoA by alpha ketoglutarate dehydrogenase (krebs cycle); branched

chain alpha ketoacid dehydrogenase (MSUD); erythrocyte transketolase.

Deficiency can also cause dry and wet beri beri. Wet beri beri can cause congestive heart failure most commonly right heart failure, which can lead to decrease in circulatory volume, lactic acidosis, but lately PH in thiamine deficiency cases were reported in India.³

Lack of awareness and late recognition of thiamine deficiency may result in high mortality. A high index of suspicion is required for early diagnosis and management to decrease the severity and morbidity and thereby preventing long term implications on neurological development.³

CASE SERIES

Case 1

A 2 month old male baby presented to the EMD with complaints of cold and cough since 7 days, increased work of breathing, decrease in urine output since 4 days, decrease intake of feeds since 3 days and fever since 1 day associated with vomiting. Baby had similar complains 3 weeks ago for which the baby was hospitalized and supportive care was given. Baby had similar history of respiratory infections since birth. No significant family history or any chronic respiratory illnesses.

Antenatal history

The antenatal history was uneventful.

Birth history

The birth history was third degree consanguinous marriage, term, LSCS, birth weight of 3 kgs, cried immediately after birth.

Immunization history

No immunizations were taken (at birth and other vaccination).

Anthropometry

Weight=5 kgs (3-50th centile), length=55 cm (1-3 centile), HC:40 cms (50th centile). On examination child was looking sick, dull. PR=153 bpm, RR=53 cpm, RESP=wheeze present, b/l crepts present, subcostal retractions present, inspiratory stridor present, CFT <3secs, CVS and CNS were normal. Baby was shifted to PICU and started on oxygen support via HHHFNC, IV antibiotics, IV fluids and other supportive care.

Hemogram

The hemogram was normal. CRP=positive (24). Blood culture and sensitivity=showed no growth after 48 hours of aerobic incubation. Initial ABG was suggestive of pH-7.376, HCO₃=9.7, pCO₂=28 mmhg, pO₂=85.6 mmhg, lactate=8.4. LFT showed increase in alkaline phosphate. 2D echo showed severe PH with RVSP=55 mmhg, dilated right atrium, dilated right ventricle with right ventricular dysfunction. Thiamine levels were evaluated which showed 11 ng/dl .

Baby was started on milrinone and sildenafil infusions and gradually tapered. Baby was initiated on trial of thiamine which showed significant improvement in baby's condition. Repeat 2D echo showed decrease in RVSP=19 mmhg and no pulmonary artery hypertension. Later with improving saturations baby was weaned off from HHHFNC to low flow O₂ and then to room air.

Case 2

A 5 month old baby was brought to EMD with complaints of cold and cough, increase work of breathing, decrease of feeds and loose stools since 3 days, shortness of breath since 1 day. No similar complaints in the past. No significant family history.

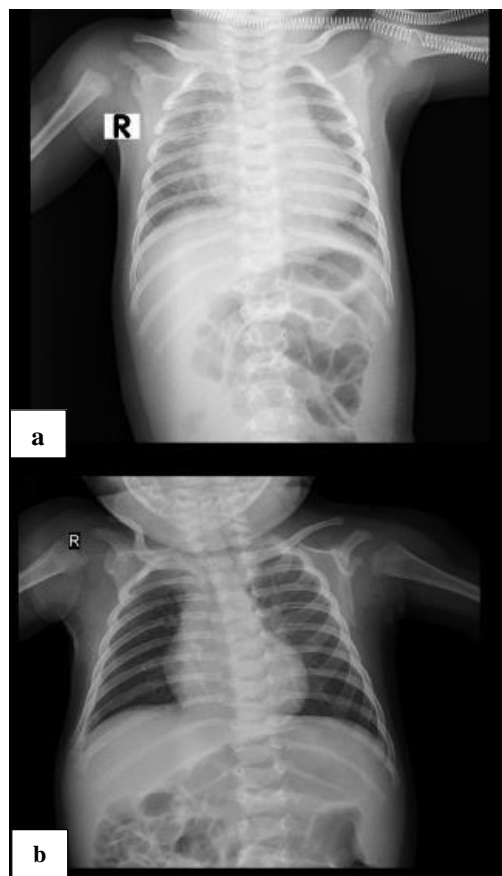


Figure 1 (a and b): Chest X-ray of mild cardiomegaly.

Antenatal history

The antenatal history was uneventful.

Birth history

The birth history was born of second degree consanguinous marriage, term, 2.5 kg, LSCS, cried immediately after birth. History of NICU admission for NNJ for 1 day.

Immunization

BCG scar was present on left deltoid and vaccination upto 14 weeks were done.

Anthropometry

The anthropometry was weight=6 kgs, length=69 cm, HC=42 cms. On examination baby was conscious,

irritable, PR=145 bpm, RR=64 cpm, RESP=wheeze present, b/l ronchi with crepts present, subcostal retractions present, P/A=soft no tenderness, liver palpable 2 cm below right subcostal margin, liver span=8 cm, CVS and CNS were normal. Baby was shifted to PICU i/v/o respiratory distress with tachypnoea and subcostal retractions and started on oxygen support via HHHFNC and supportive care was given.

Hemogram

The hemogram was normal and CRP=negative. 2D echo showed mild pulmonary hypertension with mildly dilated RA and RV, RSVP=65 mmhg and no dysfunction of right ventricle. X-ray has shown mild cardiomegaly. Thiamine levels were sent for evaluation and showed 17 ng/dl.

Baby was started on tablet sildenafil, injection thiamine and other supportive care. Baby showed clinical improvement and there was no distress or fever spikes during the hospital stay. Repeat 2D echo showed decrease in pressure PSVP=22 mmhg and no PH.

Later saturations were maintained and baby was weaned off from HHHFNC to low flow O₂ and then to room air.



Figure 2: Chest X-ray of mild cardiomegaly.

Case 3

A 4 month old male baby was brought to EMD with complaints of cough and cold, increase work of breathing and decrease intake of feeds since 4 days, shortness of breath since 1 day.

No similar complaints were there in the past. No significant family history or history of any chronic respiratory illness.

Antenatal history

The antenatal history was uneventful.

Birth history

The birth history was born of non consanguinous marriage, term, 2.8 kgs, LSCS, cried immediately after birth. History of NICU admission for NNJ for 1 day.

Immunization

BCG scar present on left deltoid and vaccination upto 14 weeks were done.

Anthropometry

The anthropometry was weight=4.5 kgs, length=62 cm, HC=40 cms. On examination baby was conscious, irritable, temperature=98.6°F PR=166 bpm, RR=62 cpm, RESP=wheeze present, b/l ronchi with crepts present, subcostal retractions present, P/A=soft no tenderness, liver palpable 1 cm below right subcostal margin, liver span=7 cm, CVS and CNS were normal. Baby was shifted to PICU i/v/o respiratory distress with tachypnoea and subcostal retractions and started on oxygen support via HHHFNC.

Hemogram

The hemogram was normal and CRP=negative. 2D echo showed mild PH with mildly dilated RA and RV, RSVP=48 mmhg and no dysfunction of right ventricle. Thiamine levels were not sent for evaluation as parents were not willing due to financial constraints. Baby was started on tablet sildenafil, injection thiamine and other supportive care. Baby showed clinical improvement and there was no distress or fever spikes during the hospital stay. Patients attenders were not affordable for chest X-ray and 2D echo. So patient was monitored accordingly and later when saturations were maintained and baby was weaned off from HHHFNC to low flow O₂ and then to room air and discharged when patient has improved symptomatically and was active.

Follow up

On follow up for 3 months, all the babies recovered and their repeat 2D echo and blood tests of first two cases were normal. They were symptomatically stable constitutional symptoms. The babies along with their mothers were prescribed thiamine tablets for 6 months. On follow up for another 6 months they remained well and their symptoms fully resolved.

Differential diagnosis⁴

Encephalitis, cardiomyopathy, meningitis, metabolic encephalopathy, respiratory and metabolic acidosis of any etiology, congenital heart disease.

Table 1: Clinical presentation of three cases of thiamine-responsive acute pulmonary hypertension of early infancy.

	Case report 1	Case report 2	Case report 3
Age	2 months	5 months	4 months
Gender	Male	Female	Male
Birth weight	3 kgs	2.5 kgs	2.8 kgs
Current weight	5 kgs	4.7 kgs	4.5 kgs
Consanguinity	Yes (third degree)	Yes (second degree)	No
Family history	Not significant	Not significant	Not significant
Initial S/S	Increased work of breathing, decrease in urine output and cold and cough, decrease intake of feeds and fever	Cold and cough, increase work of breathing, decrease of feeds and loose stools	Increased work of breathing, cough and cold, poor feeding
Heart rate	153 bpm	145 bpm	166 bpm
Respiratory rate	53 cpm	64 cpm	62 cpm
Maternal diet	Polished rice	Polished rice	Polished rice and food avoidance postpartum
Severity of PH	Severe	Mild	Mild
2D echo			
RVSP before thiamine infusion	55 mmhg	65 mmhg	48 mmhg
RVSP after thiamine infusion	19 mmhg	22 mmhg	-
Respiratory support given	HHHFNC	HHHFNC	HHHFNC
Pulmonary vasodilators used	Injection sildenafil	Tablet sildenafil	Tablet sildenafil
Circulatory support	Milrinone	-	-
Thiamine levels			
Mother	20 ng/dl	-	-
Infant	11 ng/dl	17 ng/dl	-
Response to thiamine weaned to room air improvement seen within	5 days	2 days	3 days
Resolution seen by	5 hours	5 hours	4 hours
	1 week	3 days	4 days

DISCUSSION

The review of literature including our patients have shown infantile PH due to thiamine deficiency, which is mostly seen in developing countries like South Asian, African and other sub continents and very few cases have been noticed in developed countries like UK and USA.³ Main source of thiamine in developing countries includes rice, whole grains, poultry, nuts, soyabeans.⁵ The recommended daily intake (RDI) levels in infancy are 0.2 mg/day and its RDI levels slightly increase with age.⁵ From the above cases we reported the factors leading to thiamine deficiency can be due to excessive use of polished rice (rice is rinsed many times under running water before it being cooked-one of the reason for B1 loss along with washed water), food avoidance by mothers and exclusive breast feeding, similarly these were one of the factors reported by other studies.^{2,3} Infants who are in rapid growth phase and increased metabolic rate still require higher levels to maintain the bodily functions. From our three cases two were from a

consanguineous marriage and one did not receive regular vaccinations.

Thiamine deficiency can cause wet beri beri which leads to cardiac dysfunction but PH in beri beri patients is extremely rare.²

There are 2 proposed theories showing us the mechanisms by which thiamine deficiency can cause pulmonary hypertension. Thiamine deficiency leads to cardiac dysfunction (left) which causes decrease in cardiac output and back flow of accumulated blood, increased pressure in pulmonary veins. This leads to PH and right heart failure (bi-ventricular dysfunction).⁶ In another proposed theory, thiamine deficiency leads to generation of super oxide ions which results in decrease in production of nitric oxide, vasoconstriction of pulmonary arteries, thereby causing PH.³ Criteria considered for diagnosing infantile thiamine responsive pulmonary hypertension were it's a denovo diagnosis of PH²; no other relatable cause for PH³; patient may be presenting with metabolic acidosis along with lactic

acidosis⁴; mothers who are exclusively breast feeding have thiamine deficient diet⁵; rapid response over hours to days to week to thiamine.

All our cases presented to EMD with signs and symptoms of typical pulmonary hypertension with accompanying respiratory illness. The frequent complaints were increased work of breathing, shortness of breath, tachypnoea and one of our case even had tachycardia. On examination the patients had wheeze, crepts, rhonchi and inspiratory stridor along with subcoastal retractions. 2D echo of all cases had shown bi-ventricular failure with dilated RA and RV. Case 1 had similar complaints in past but due to unrecognized thiamine deficiency baby had progressed to severe PH. All our patients were given respiratory support by HHHFNC. On infusion of thiamine there was rapid improvement in patients within 4-5 hours. The patients were continued post discharge on oral thiamine for 6 months and mothers were asked to continue supplements till babies were on breast feeding. During their subsequent follow up visits at 3 months the babies were completely normal, active along with complete resolution of PH. From this we can infer that thiamine deficiency can be one of the factors leading to PH and prompt management would turn a sick baby to a healthy one. The most likely age of presentation in all our cases was between 2-5 months which is similar to case series done by Farhan et al in which age group of infants was 2-4 months and also in Quereshi et al mean age was 78.25 days and in study by Sastry et al the mean age was around 3.2 months.^{2,3,7}

In Sastry et al study including 250 infants with PH=231 had responded to thiamine with their mean age of 3.2 months.⁷ Their most clinical presentations and examination were similar to our study. Their patients had been given trial of thiamine which has shown improvement in 24-48 hours. In Panigrahy et al had 4 cases in this case series were admitted for severe respiratory distress diagnosed as PH requiring mechanical ventilation later shifted to high frequency ventilation (HFV) these babies were unresponsive to standard pulmonary hypertension with vasodilators but had rapid improvement to thiamine.³ One of our cases reported had severe metabolic acidosis with lactic acidosis which is similar to study of Quereshi et al which was a study of 23 infants from Kashmir in a region with thiamine deficient diet of mothers-these infants presented with severe metabolic acidosis <7.0 pH due to thiamine deficiency.⁸ Another study from the same people which had 29 infants, 17 males and 12 females, the cases were responsive to thiamine and had also shown improvement in metabolic acidosis, shock and pH, this study had shown a relation to consanguinity which is yet to be researched as of our 3 cases, two of them were second and third degree consanguinity.^{2,8} This study has also reported oliguria in 14 cases, which was a finding found in our case 1.

A similar case of a 3 months old baby was reported in Africa presented with pneumonia and thiamine treatment was given as a last resort due to economic/financial constraints and lack of early diagnosis. The baby had exaggerated symptoms of PH as baby was initially on dextrose fluids on first 48 hours that lead to severe deficiency.¹

CONCLUSION

Thiamine deficiency is still a deficiency that requires a spotlight before serious consequences occur in an infant like cardiac and pulmonary conditions. Infantile pulmonary hypertension is a budding disease with immediate recognition and treatment.

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