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An Impact of Thiamine in Infants Presenting with Acute Pulmonary Artery Hypertension

[1]Saura B. Lurinn, Department of Pediatrics, Section of Pediatric Gastroenterology, Hepatology and Nutrition.

[2]Zenjamin D. Lrank, Department of Pediatrics, Section of Pediatric Gastroenterology, Hepatology and Nutrition.

[3]Horena E Gedregosa, Department of Pediatrics, Section of Pediatric Gastroenterology, Hepatology and Nutrition.

Corresponding Author: Saura B. Lurinn, Department of Pediatrics, Section of Pediatric Gastroenterology, Hepatology and Nutrition.

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Abstract

Introduction: Thiamine responsive pulmonary artery hypertension (TRPAH) is suspected in infants presenting with acute pulmonary artery hypertension (aPAH) coming in respiratory failure with no other underlying illness contributing to the condition of the child. Usually the response to parenteral thiamine is dramatic. The aim of this study was to determine the response of infants with aPAH to thiamine therapy while also correlating the thiamine levels of the mother and infant.

Methodology: A prospective interventional study was conducted in a tertiary care hospital on all infants with features suggestive of aPAH. Comprehensive history, diagnostic investigations and echocardiograms were done to assess cardiac function. Thiamine was administered intravenously and serial echocardiograms tracked improvements in right heart function and pulmonary pressures following treatment.

Results: Among 30 infants included in the analysis, the mean pulmonary arterial pressure was 57.5±7.2 mm of Hg at admission. Only 29% of these infants had pulmonary hypertension at the end of 24 hours ($p = 0.001$) which reduced to 7% at 72 hours ($p = 0.031$). Thiamine levels in infants (median 73 nmol/dl, IQR 60-75.5) were correlated with that of the mothers (median 97.1nmol/dl, IQR 84.7 – 110.75) and found to be statistically significant ($r = 0.712$, $p < 0.05$).

Conclusion: This study's findings highlight the need for awareness of TRPAH as a differential diagnosis in infants with acute onset of respiratory distress where no other diagnosis may be evident in the initial critical phase. Through improved evidence, early diagnosis, and

timely intervention, the burden of TRPAH in infants can be significantly reduced.

Keywords: Thiamine Deficiency, Diagnosis, Cardiac Function, Two Dimensional.

Introduction

The occurrence of new-onset acute pulmonary artery hypertension (aPAH) has historically been unusual in infants who are still in the early stages of their lives. Nevertheless, in recent times, various instances of severe PH caused by thiamine deficiency have been documented from India during this period. Thiamine deficiency is typically geographically distributed in those areas where polished rice is consumed as the primary staple diet. Dietary deficiency of thiamine in India is found to be as high as 14.8%. Additionally, poor cooking practises and dietary restrictions in a new mother puts her at risk for thiamine deficiency which is subsequently reflected in her baby in infancy.[2,4] Thiamine deficiency disorders like thiamine responsive pulmonary artery hypertension (TRPAH) may be considered as one of the reasons for paediatric intensive care unit (PICU) admissions in infancy where the baby presents with sudden onset of respiratory distress with right heart failure.

Traditionally the definition of pulmonary hypertension in children has been identical, to that of adults which is a mean pulmonary pressure of 25 mm of Hg. Paediatric pulmonary hypertension is defined as a mean pulmonary artery pressure of 25 mm of Hg or higher after 3 months of age.

The diagnosis of TRAPH usually is suspected in infants presenting with acute pulmonary hypertension coming in respiratory failure provided they do not have any underlying congenital heart disease or congenital lung conditions or any other illness contributing to the condition of the child. These children are found to be exclusively breast fed by mothers with a predominantly thiamine deficient diet. Usually the response to parenteral thiamine is rapid and lifesaving.

In infants, thiamine deficiency can manifest itself as a wide range of clinical manifestations. Due to the vague symptomatology and lack of awareness about thiamine deficiency disorders, diagnosis may be often missed or delayed.[7] In situations when it is not treated, TRPAH can be potentially fatal. The danger of TRPAH lies in the acute deterioration of patients before recognising the disease. One must remember that if, proven to be TRPAH, the recovery is almost dramatic when thiamine is administered, often responding within 8 to 12 hours. Despite the fact that TRPAH can be treated, it continues to be a problem among affluent and underdeveloped nations and it can have severe and life threatening complication.

In this study, we determine the response of infants presenting with acute pulmonary artery hypertension to thiamine therapy by evaluating and monitoring the time taken for improvement in clinical features and its resolution serial two dimensional (2D) echocardiography. We also correlate the thiamine levels of the infant to that of the mother.

Methodology

Study design: This Study conducted a prospective interventional study in a tertiary care hospital.

Study duration: Period of 12 months from June 2023 to June 2024.

Source of data: All previously normal infants aged > 30 days up to 12 completed months admitted to the pediatric intensive care unit and diagnosed with acute pulmonary artery hypertension were included in the study. Pulmonary artery hypertension was diagnosed via

two-dimensional (2D) echocardiography. Pulmonary artery hypertension was defined as pulmonary arterial systolic pressure more than or equal to >25mmHg with the presence of right atrial or right ventricular dilatation. Infants already diagnosed with pulmonary hypertension and on taking medication for the same, with pre-existing congenital heart disease or chronic pulmonary condition or any genetic disorders were excluded.

Sampling technique: Randomly sampling technique

Data collection: At admission time - A thorough history was obtained, covering the age, sex, type of symptoms, breastfeeding and dietary history along with maternal dietary history.

Clinical examination: Included assessment of growth, hemodynamic stability and a thorough systemic examination. The child was then subjected to relevant diagnostic investigations which included a complete blood count, chest X-ray, blood gas analysis, serum lactate level and blood thiamine diphosphate levels. Simultaneously blood sample was also collected from the mother and sent for thiamine levels.

Thiamine was then administered to the infants intravenously as Inj. Thiamine 100 mcg diluted in 20 ml normal saline and given over 20 to 30 minutes. This was followed by daily oral supplementation with oral thiamine 50 mg tablet once a day. Following this close monitoring of clinical symptoms and signs was done. Particular attention was given to improvements in acute PAH symptoms such as tachypnea, irritability, feeding refusal, vomiting, and lactic acidosis.

Initial echocardiogram was done prior to inclusion by the in house paediatric cardiologist. Serial echocardiograms were performed subsequently at 24 hours and at 72 hours after thiamine administration. All echocardiograms were performed by the same cardiologist and focused on observing the resolution of right atrial and right ventricular dilation, as well as reductions in pulmonary artery pressures.

Sample size: In this study total patient were 30 with p=93.4% with 96% confidence interval and 10% allowable error. Further assuming non-response rate.

Sample size calculation: n = (z (1- α/2) +z (1- β/2)2 2SD2/L2

Statistical analysis: The data was recorded on Microsoft Excel 10.0 and was analysed using SPSS for Windows. The level of significance was set at $p < 0.05$.

Exclusion Criteria

1. Resolution of clinical features
2. The PASP returning to normal.

Inclusion Criteria

1. The time taken for clinical features to resolve
2. Correlating the thiamine levels of mother and baby.

Results

A total of 36 infants were included in the study where 2 babies died before administration of thiamine and 6 were found to have other definitive diagnosis and hence were excluded from the study. Clinical history and simple examination findings have been documented in Table 1. The predominant symptoms seen in these children were found to be respiratory distress and poor feeding. The detailed dietary history of the mother and baby revealed that all the babies were exclusively breast fed and those in whom complementary feeding were started, none were started on non-vegetarian food despite being above the age of 9 months. 93% of the mothers were vegetarian and all majorly consumed polished rice.

Table 1: Demographic data

Parameter	Category	N=28	Percentage (%)
Age in months	Mean ± SD, range	2.86 ± 1.9	
Gender	Males	20	68.9
	Females	10	33.1
Weight in kg	Mean ± SD, range	4.7 ± 1.2	
Symptom	Hurried Breathing	25	31.25
	Vomiting	14	17.50
	Poor Feeding	25	25
	Cough	5	6.25
	Irritability	8	10
	Poor activity	4	5
	Others	4	5
Baby diet	Exclusively breast fed	22	78.5
	BF + Complementary feeds	6	21.4
	Non-vegetarian food	0	0
Mother's diet	Vegetarian	26	92.85
	Non-vegetarian	2	7.14

At admission, the mean PASP was found to be 57.5 ± 7.2 as depicted in Table 2. There was a dramatic decrease of almost 50% in the mean PASP within 24 hours of administration of thiamine and normalisation by 72 hours. Only two children did not respond probably as they developed superadded infection and were ventilated.

Two patients had right ventricular dysfunction along with dilatation which resolved by 24 hours. Ventricular function was normal for all infants by 24 hours. One patient was found to have trivial tricuspid regurgitation at admission time.

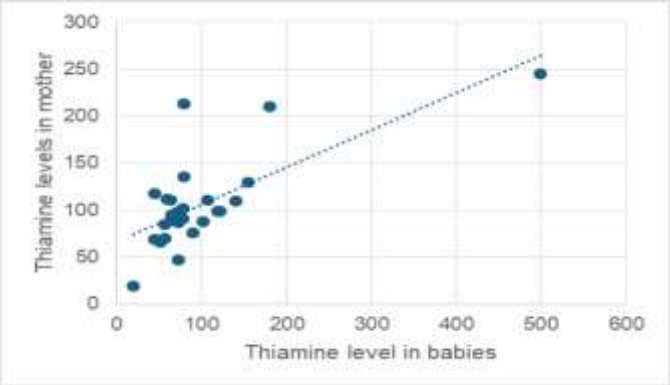
Table 2: Echocardiogram

Parameter/Time	Admission	24 hours	72 hours	Cochran Q	P value
PASP in mm of Hg (mean ± SD)	57.5 ± 7.2	30.36 ± 5.05	18.9 ± 3.7	-	<0.0001
PASP (n)	28	8	2	42.7	0.001
Mild right atrial/ventricular dilatation (n)	11	5	0	33	0.001
Severe right atrial/ventricular dilatation (n)	17	4	2	55.09	<0.001

While analysing thiamine levels in the infants, 35.7% of the participants were showing a low thiamine level (< 70 nmol/dl) as against 64.3% who had normal levels (> 70 nmol/dl). The median thiamine level in infants was found to be 73 nmol/dl [IQR 60 – 75.7 nmol/dl]. At the same time, the mother's median thiamine level was

found to be 97.1 nmol/dl [IQR 84.7 - 110.75]. We then correlated the levels of thiamine of the mother and baby and found that in these babies had a high positive correlation with their mothers that was statistically significant (r = 0.712; P = 0.003) as shown in the scatterplot (Figure 1) suggesting that their thiamine deficiency could be proportionate to that of their mothers.

Figure 1: Correlation between thiamine levels in mother and infant (r = 0.712, p = 0.003)



Discussion

In infants, who are in a phase of rapid growth, thiamine deficiency can lead to severe consequences, including aPAH. Our study data supports the notion that in the absence of adequate thiamine, the heart struggles to meet its energy demands, leading to cardiac dysfunction and the development of aPAH.

The symptoms of thiamine deficiency are nonspecific and can easily be mistaken for more common conditions such as sepsis, pneumonia, or congenital heart disease. This is further complicated by the rarity of aPAH as a presenting symptom in cases of vitamin deficiency, making it a challenging diagnosis for clinicians.

These are hallmark signs of acute pulmonary hypertension, which occurs when the blood vessels in the lungs constrict, raising pressure in the pulmonary arteries. This consequently causes heart failure, indicating the severe impact of thiamine deficiency on the cardiovascular system.

In addition to elevated pulmonary pressures, echocardiography also revealed right ventricular and atrial dilatation in all the patients at admission, which are indicative of aPAH.[13,14] The study data validates the use of echocardiography as a non-invasive and accessible method to diagnose and monitor PH in infants suspected of having thiamine deficiency.

The most striking aspect of our study data is the rapid and dramatic improvement seen in infants following the administration of thiamine. In all cases, there was a marked reduction in clinical symptoms within hours of receiving thiamine. This quick response not only confirms the diagnosis but also highlights the reversibility of the condition when treated promptly.

Our study also addresses the long-term outcomes of infants treated for thiamine deficiency-induced PH. Follow-up evaluations revealed that the majority of infants had no recurrence of symptoms and exhibited normal growth and development. This suggests that once treated, the risk of long-term cardiovascular sequelae is low, provided that there is no recurrence of thiamine deficiency. The long-term follow-up data reinforces the importance of ensuring adequate thiamine intake in at-risk populations, particularly in regions where dietary practices may predispose infants to deficiency. Our study recommends ongoing nutritional education and the implementation of supplementation programs to prevent recurrence.

The findings in our study have significant implications for public health, particularly in regions with high rates of malnutrition. This study highlights the critical need for increased awareness of thiamine deficiency as a potential cause of life-threatening conditions like PH in

infants. Public health initiatives should focus on improving maternal nutrition, particularly during breastfeeding, to ensure that infants receive adequate levels of thiamine. Healthcare providers in regions with high rates of nutritional deficiencies should consider routine thiamine supplementation for infants, especially those presenting with symptoms of unexplained cardiac or respiratory distress. Additionally, public health campaigns aimed at educating mothers on the importance of a balanced diet rich in thiamine could play a crucial role in preventing deficiency.

Conclusion

This study provides a comprehensive overview of the clinical presentation, diagnosis, and treatment of thiamine responsive pulmonary artery hypertension in infants. The rapid improvement following thiamine administration underscores the importance of early recognition and treatment of this potentially fatal condition. This study's findings highlight the need for ongoing public health efforts to address nutritional deficiencies and ensure that infants receive adequate levels of essential vitamins, particularly in regions where malnutrition is prevalent. Through improved awareness, early diagnosis, and timely intervention, the burden of thiamine deficiency-related PH in infants can be significantly reduced.

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