



A Study of Blood Thiamine Levels in Infants with Pulmonary Hypertension

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Abstract

Introduction: Pulmonary hypertension (PH) has been linked to significant morbidity and mortality for a long time in children. The causes of pulmonary hypertension have different mechanisms. Over the past few years there has been a rise in the incidence of acute pulmonary hypertension, more in the infant age group. Some studies have shown that this clinical presentation overlaps with that of infantile thiamine deficiency and that intravenous administration helps with rapid recovery. Through this study we wanted to correlate blood thiamine levels with pulmonary hypertension in infants.

Methods: This study was conducted among 30 infants admitted in JSS hospital, Mysuru over a period of 18 months. Among these, 15 were taken as cases with pulmonary hypertension, 15 as controls without pulmonary hypertension and thiamine status of all of them were estimated. Two milliliter of blood was sent in EDTA vacutainer for testing for thiamine pyrophosphate by LCMS method.

Results: The mean age of study population was 4.93 (+/- 2.70) months, with male predominance of 80%. A significant correlation between thiamine levels and PH was found in this study, with a strong to moderate negative correlation by using Pearson correlation coefficient.

Conclusions: This study concludes that there is significant correlation between thiamine and pulmonary hypertension, and thiamine may be used as a variable in identification of acute pulmonary hypertension in infants.

Introduction

Thiamine, also known as vitamin B₁, is a vitamin, an essential micronutrient, that cannot be made in the body.¹ Thiamine diphosphate, the active form of thiamine, serves as a cofactor for several enzymes involved in carbohydrate catabolism such as pyruvate dehydrogenase, transketolase, and α -ketoglutarate. It helps in synthesis of acetylcholine and γ -aminobutyric acid (GABA) which have important role in nerve conduction. Thiamine is primarily transported in erythrocytes and delivered to areas of high metabolic demand in the brain, heart, liver, pancreas, muscles, and nerves.^{2,3} Thiamine deficiency has been described as a spectrum which shows varied types of presentations at different ages⁴ as shown in Fig. 1.

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Figure 1: Clinical spectrum of thiamine deficiency disorders⁴

Acute Cardiologic Form	Aphonic Form	Pseudo Meningitic Form	Encephalopathy	Peripheral Neuropathies
<ul style="list-style-type: none"> • Peak prevalence in breastfed babies of 1–3 months of age • Colic • Restlessness • Anorexia • Vomiting • Edema • Cyanosis and breathlessness with signs of heart failure leading to death • Pernicious form or Shoshin Beriberi • Sudden cardiogenic shock 	<ul style="list-style-type: none"> • Peak prevalence in 4- to 6-month-old infants • Initially hoarse cry until no sound is produced while crying • Restlessness • Edema • Breathlessness and death 	<ul style="list-style-type: none"> • Peak prevalence in 7- to 9-month-old infants • Nystagmus (involuntary eye movement) • Muscle twitching • Bulging fontanelle • Convulsions • Unconsciousness 	<ul style="list-style-type: none"> • Generally older children or adults but also seen in infants • Psychomotor slowing or apathy • Nystagmus or ophthalmoplegia • Ataxia • Impaired consciousness • Eventually coma and death 	<ul style="list-style-type: none"> • Older children or adults • Pain • Tingling or loss of sensation in hands and feet (peripheral neuropathy) • Muscle wasting with loss of function or paralysis of the lower extremities • Loss of ankle and knee reflexes • Cranial nerve impairment

In a thiamine-deficient state, the earlier mentioned enzymes limit supply to and cycling of the Krebs cycle, resulting in decreased adenosine triphosphate (ATP) synthesis, oxidative damage, and cell death. Metabolic disturbances in thiamine deficiency lead to metabolic acidosis, and laboratory evaluation will often reveal an elevated lactate concentration.

Cardiomyocytes require a constant supply of energy and aberrations in aerobic respiration pathways caused by thiamine deficiency interrupt normal heart functioning which may be problematic. This is compounded by endovascular dysfunction because of thiamine-dependent nitric oxide synthase,⁵ an enzyme which is also implicated in the lungs of patients with PH. So, in thiamine deficiency the culmination of the disturbances is PH and often right-predominant heart failure.

Two mechanisms have been speculated for PH in these infants with thiamine deficiency. The first mechanism is that of pulmonary venous hypertension. It occurs as a result of progressive energy failure and / or damage to the myocardium that leads to circulatory breakdown, lactic acidosis and left ventricular dysfunction leading to elevated 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. The second mechanism is through the production of superoxide anions and other reactive oxygen species (ROS) and reactive nitrogen species (RNS). Thiamine deficiency is associated with increased production of ROS. Superoxide anions can inactivate nitric oxide producing peroxynitrite, a powerful vasoconstrictor that can exacerbate PH.

Hence this study was done to check the correlation between thiamine levels and PH to ascertain for the above-mentioned mechanisms.

Methods

This was a cross-sectional study conducted at Jagadguru Sri Shivarathreeshwara (JSS) Medical College, Mysore, India from January 2021 to June 2022. We estimated the minimum sample size for the study based on incidence of PH reported in an earlier Indian study.⁶ Data was collected by purposive sampling technique. Infants in the age group of three to 12 months admitted in the Department of Paediatrics with tachypnoea (Respiratory rate > 50 breaths / min) were screened and selected.

Routine blood investigations, blood gas analysis and chest radiograph were done in all. Infants with gross abnormalities on chest radiograph, i.e., empyema, lung abscess, severe pneumonia (as per WHO definition), pleural effusion, pneumothorax, hydrothorax were excluded. Infants eligible for the study were subjected to 2D Echocardiogram. Any infant with evidence of congenital heart disease was also excluded from the study.

Infants with tachypnoea and RVSP > 25 mm Hg on 2D Echo cardiogram were taken as cases and infants with tachypnoea and RVSP < 25 mm Hg on 2D Echo cardiogram were taken as controls. Blood sample for thiamine levels were sent for these 30 infants at admission itself (RVSP = PASP in the absence of stenosis). The levels sent were tested by Liquid chromatography-mass spectrometry (LC-MS) which is an analytical chemistry method that combines mass spectrometry's mass analysis capabilities with liquid chromatography's physical separation abilities. Data were entered into a SPSS spreadsheet. Mean with standard deviation, was calculated for variables of age, RSVP and thiamine levels in both groups. A difference of P value < 0.05 was taken as significant. In this study, Pearson correlation coefficient (r) was used to measure the linear correlation between PASP and thiamine values. A binary logistic regression was also done to quantify the results.

Results

In infants with PH (cases) group, mean ± standard deviation age was observed to be 4.93 ± 2.70 months and median age was 3.5 months. Both cases and controls were age matched. 80% of cases and controls belong in the age group between three to six months.

Table 1: Age-wise distribution of infants in case and control group

Age group (months)	Cases		Controls		p-value
	No.	%	No.	%	
3 to 6	12	80	12	80	1.0
> 6 to 9	2	13.33	2	13.33	
> 9 to 12	1	6.67	1	6.67	
Total	15	100	15	100	

In both groups male patients were predominant; in the case group; male patients comprised 80% of patients and 20%

patients were females.

In the control group, males comprised 60% of patients and 40% patients were females. Difference in gender distribution of patients in both groups was not found to be statistically significant (P = 0.204).

Table 2: Gender-wise distribution of infants in case and control group

Gender	Cases		Controls		p-value
	No.	%	No.	%	
Females	3	20.00	6	40.00	0.204
Males	12	80.00	9	60.00	
Total	15	100	15	100	

Among infants in the case group; the mean ± standard deviation pulmonary artery pressure was observed to be 77.53 ± 18.68 mmHg, the median pulmonary artery pressure was 75 mmHg, and the range was 69.00.

In control group the mean ± standard deviation pulmonary artery pressure was observed to be 24.07 ± 2.28 mmHg, the median pulmonary artery pressure was 24 mmHg. Infants in the case group had a considerably higher mean pulmonary artery pressure than infants in the control group with a p-value of < 0.05.

Table 3: Descriptive statistics of pulmonary artery pressure of patients in case and control group

Pulmonary Artery Pressure (mmHg)	Cases (N = 15)	Controls (N = 15)	t-test p-value
Mean ± SD	77.53 ± 18.68	24.07 ± 2.28	< 0.05
Median	75	24	
Inter quartile range	22	3	
Maximum	124	28	
Minimum	55	20	

The mean ± standard deviation blood thiamine levels among cases and control group has been depicted in the table 4.

Table 4: Descriptive statistics of thiamine levels of patients in

case and control group

Thiamine levels (µg / L)	Cases (N = 15)	Controls (N = 15)	t-test p-value
Mean	24.94	52.12	< 0.01
Median	26.39	44.00	
Standard Deviation	11.99	19.1	
Range	45.68	73.48	
Interquartile range	10.7	17.8	
Minimum	3.72	39.30	
Maximum	49.40	112.78	

Mean blood thiamine levels were lower in patients in the case group as compared to patients in the control group. The difference in the mean blood thiamine levels among patients of the case and control group was found to be highly significant statistically ($p < 0.001$). Correlation was checked using Pearson correlation coefficient. The 'r' value was -0.533 which is significant at the level of 0.01.

And to quantify this, binary logistic regression was done which showed that the odds of increasing pulmonary hypertension with 1 unit decrease in thiamine level is 25.10%.

ROC curve has also been drawn to check how far thiamine levels can be used as a diagnostic test or predictor for PH in infants. Area under the curve shows a value of 0.942.

Table 5: Correlation between ECHO PASP and thiamine levels

Pearson Correlation			
		ECHO-PASP (mm of Hg)	Thiamine levels (mu / L)
ECHO-PASP (mmHg)	Pearson Correlation	1	$-.533^{**}$
	Sig. (2-tailed)		0.002
	N	30	30
Thiamine levels (mu / L)	Pearson Correlation	$-.533^{**}$	1
	Sig. (2-tailed)	0.002	
	N	30	30

** Correlation is significant at the 0.01 level (2-tailed)

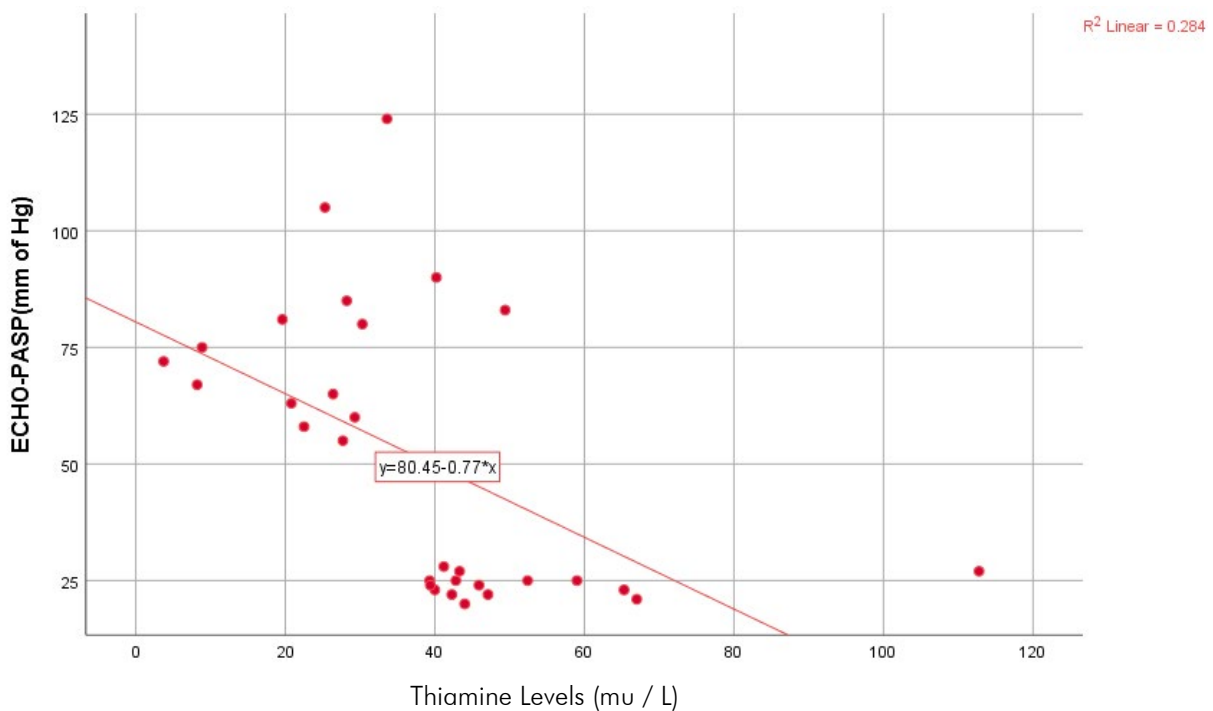


Figure 2: Correlation between ECHO-PASP and thiamine levels

Table 6: Binary Logistic regression between thiamine levels and pulmonary hypertension

Binary		B	Exp(B)	Sig.	95% C.I. for Exp (B)		Odds of increasing pulmonary hyper-tension with 1 unit decrease in thiamine level
logistic regression					Lower	Upper	25.10%
	Thiamine levels (mu / L)	- 0.289	0.749	0.011	0.599	0.937	
	Constant	10.894	53860	0.015			

Table 7: ROC Curve between thiamine levels and pulmonary hypertension

Area Under the Curve				
Test Result Variable(s):	Thiamine levels(mu/L)		Asymptotic 95% Confidence Interval	
Area	Std. Error ^a	Asymptotic Sig. ^b	Lower Bound	Upper Bound
0.942	0.047	0.000	0.851	1.000

a. Under the nonparametric assumption
 b. Null hypothesis: true area = 0.5

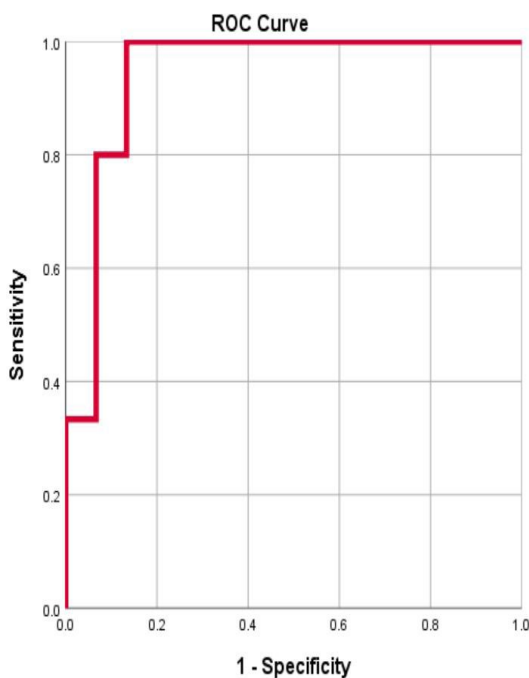


Figure 3: ROC Curve between thiamine levels and pulmonary hypertension

Discussion

In our country, our staple food consists mostly of rice and rice-

based dishes such as idlis and dosas. Most of the time it is polished white rice. It has been showed in a lot of studies that polished white rice is one of the main causes of thiamine deficiency.⁷ In the present study infants less than six months in the cases group were exclusively breastfed by mothers. The results of this study can substantiate retrospectively that the diet of these mothers was presumably thiamine deficient.

In a recent case series,⁶ all infants with thiamine deficiency and PH were exclusively breast fed and maternal diet comprised of polished, washed, white rice / exclusive breastfeeds. A term “Thiamine Responsive Acute Pulmonary Hypertension of Early Infancy” has been used to describe infants with the above-mentioned findings from this study.

In a South Indian study⁸ customary maternal dietary restrictions were present and commonly consumed breakfast made of combination of pulses and cereals were not permitted.

The risk of thiamine deficiency is higher in mothers who eat only polished white rice that has been rinsed several times. The greatest risk for developing thiamine deficiency is in young infants (One to three months of age) who are exclusively breastfed by thiamine deficient mothers.⁶ Poor thiamine intake may be due to losses from food due to cooking practice and dietary restrictions.

In infants and children, the spectrum of thiamine deficiency is varied, from restlessness and breathlessness to convulsions and encephalopathy.⁴ The most severe one in infants being

Shoshin beri-beri. PH was not usually associated with thiamine deficiency as echo was not done regularly. Now it has been shown that high cardiac output failure with imbalance of mitochondrial energetics, reactive oxygen and nitrogen species has given rise to such a presentation.⁶ By administering thiamine in such cases, response has been observed as soon as within PH.⁸

In the present study infants with PH were observed to have significantly lower mean serum thiamine levels $24.94 \pm 11.99 \mu\text{g} / \text{L}$ or $73.95 \pm 35.55 \text{ nmol} / \text{L}$ compared to infants in control group without PH where mean levels were $52.12 \pm 19.10 \mu\text{g} / \text{L}$ or $154.5 \pm 56.63 \text{ nmol} / \text{L}$.

In this study, Pearson correlation coefficient (*r*) was used to measure the linear correlation between PASP and thiamine values. The '*r*' value was $-.533$ which is significant at the level of 0.01. It says that there is strongly to moderate negative correlation between thiamine levels and PASP. It means that with decrease in thiamine levels, an increase in pulmonary pressures has been observed.

And to quantify this, binary logistic regression was done which showed that the odds of increasing PH with one unit decrease in thiamine level is 25.10%.

ROC curve has also been drawn to check how far thiamine levels can be used as a diagnostic test or predictor for PH. Area under the curve shows a value of 0.942 and hence it is an outstanding variable to use in the identification or diagnosis of PH.

The reference values taken for thiamine pyrophosphate has been different in various studies with the lower limits varying from 39 to 98 nmol / L and upper limits being between 180 to 200nmol / L.⁹⁻¹⁴ The normal reference values of thiamine for this study were taken as 33.1 - 60.7 mic / l (98.1 – 180 nmol / L).⁹

In this study, three babies in cases group had thiamine value above 98.1 nmol / L, and two babies in controls had values above 180 nmol / L. So though 80% cases with PH have thiamine deficient value, none of the controls happen to have values below the lower limit.

Through this statistical evidence we can say that development of PH is no more an unknown outcome of infantile beri-beri. But at the same time there is a need for standardized reference values of thiamine according to the geographical distribution, diet, and practices of the communities.

Conclusions

Through our study we can say that most of the affected age group with PH happens to be in between three to six months of age. Males appear to be more at risk, but a bigger sample size may be needed to prove its statistical significance. There is a statistically significant correlation between PH and thiamine deficiency and thiamine levels can be used as a predictor of PH. As the population in general happens to be deficient in Thiamine, not all infants had symptoms of PH, which suggests that maybe the reference values for thiamine must be revised.

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Conflict of Interest: None

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