Thiamine-responsive acute severe pulmonary hypertension in exclusively breastfeeding infants: a prospective observational study

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Received 31 December 2019

Revised 20 July 2020

Accepted 2 August 2020

Published Online First

3 September 2020

ABSTRACT

Objectives Severe pulmonary hypertension (PH) causing right heart failure can occur due to thiamine deficiency in exclusively breastfeeding infants. This study describes the clinical profile and management of thiamine-responsive acute pulmonary hypertension.

Methods A prospective observational study of infants presenting with severe PH without any other significant heart or lung disease. History of symptoms, clinical examination, echocardiography and basic investigations were performed. Dietary patterns of mothers were recorded. Thiamine was administered and serial echocardiography was performed.

Results A total of 250 infants had severe PH and 231 infants responded to thiamine. The mean age was 3.2 ± 1.2 months. Fast breathing, poor feeding, vomiting and aphonia were the main symptoms. Tachypnoea, tachycardia and hepatomegaly were found on examination. Echocardiogram revealed grossly dilated right heart with severe PH. Intravenous thiamine was administered to all the babies based on clinical suspicion. Clinical improvement with complete resolution of PH was noticed within 24–48 hours. Babies were followed up to a maximum of 60 months with no recurrence of PH. All the mothers consumed polished rice and followed postpartum food restriction.

Conclusion Thiamine deficiency is still prevalent in selected parts of India. It can cause life-threatening PH in exclusively breastfeeding infants of mothers who are on a restricted diet predominantly consisting of polished rice. It can contribute to infant mortality. Thiamine administration based on clinical suspicion leads to remarkable recovery. High degree of awareness and thiamine supplementation in relevant geographical areas is required to tackle this fatal disease.

BACKGROUND AND RATIONALE

Thiamine deficiency historically was seen in refugee populations and geographical areas where rice was the staple diet. Industrialisation in developed countries has led to food fortification reducing micronutrient deficiencies. Widespread availability of polished rice in developing countries has resulted in thiamine deficiency.¹ Infantile beriberi is prevalent in South East Asian countries of Cambodia, Laos, Thailand and Myanmar. It can present as acute cardiac failure. In a recent verbal autopsy, 50% of mortality before 6 months of age might have been

What is already known on this topic?

- ▶ Thiamine deficiency can occur in exclusively breastfeeding infants. Consumption of staples with low thiamine content and postpartum food restrictions by mothers may be causative. This leads to acute right heart failure with high infant mortality rate around the third month of life.

What this study adds?

- ▶ Clinical profile of infants with severe thiamine responsive pulmonary hypertension is described.
- ▶ Echocardiographic documentation of severe pulmonary hypertension and rapid improvement with thiamine administration is demonstrated in a large cohort. Clinical clues for empirical initiation of thiamine are suggested.

associated with beriberi in parts of Cambodia. 17% of under-five mortality in Myanmar is attributed to beriberi.^{2,3} In 1990, beriberi caused 40% of infant mortality among Karen refugees in Thailand.² Pockets of infantile beriberi have been described from India.^{4–6} Consumption of polished rice, postpartum food restriction, thiaminase-containing foods such as tea, coffee or betel nut precipitate thiamine deficiency.^{7,8} Thiamine is very low in breast milk of thiamine-deficient mothers putting exclusively breastfeeding infants at high risk.⁹

In the past 6 years, we have seen previously healthy, exclusively breastfeeding infants presenting with acute cardiac failure and severe pulmonary hypertension (PH). Thiamine administration produced dramatic recovery in these sick infants.

OBJECTIVE

The manuscript seeks to describe the sociodemographic, clinical and echocardiographic features and management of thiamine-responsive acute pulmonary hypertension (TRAPH). The causal role of cultural and economic factors in thiamine deficiency is emphasised. The intermediate and short-term follow-up is presented.

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To cite: Sastry UMK, M J, Kumar RK, et al. *Arch Dis Child* 2021;**106**:241–246.

Original research

Design

A prospective observational study was undertaken from January 2013 to November 2019.

Setting

The study was conducted in paediatric cardiac unit of a tertiary-care, public hospital in southern India serving a population of 65 million from the state of Karnataka and neighbouring states. The hospital provides highly subsidised care for the poorer sections of the society.

Patients

All exclusively breastfeeding infants with severe PH diagnosed by echocardiography. Severe PH was defined as pulmonary artery systolic pressure (PASP) more than 50 mmHg as measured by tricuspid regurgitation (TR) jet with the presence of dilated right atrium (RA) and right ventricle (RV). Comprehensive echocardiogram was performed with specific focus to exclude aetiologies of PH like left-to-right shunts, coarctation, unilaterally absent pulmonary artery and left heart disease like mitral stenosis, pulmonary vein stenosis or left ventricular dysfunction. Infants with lung disease and syndromic infants with suspected genetic disorders were excluded from the study. Thiamine levels were not done as RBC transketolase activity reflective of thiamine status is not easily available. The dramatic clinical response to thiamine was inferred as diagnostic of thiamine deficiency.

Detailed history of symptoms, birth and postnatal history were taken. Development and immunisation history was obtained. Answers for focused questions on maternal dietary patterns of predominant staple consumed, milk consumption and food taboos were elicited. Assessment of growth and development was done. Haemodynamic status and systemic examination were performed daily. Chest X-ray, complete hemogram, thyroid and renal functions were performed. Comprehensive echocardiogram was carried out as per the protocol (online supplementary table 1—ECHO Protocol).

Interventions

The babies were admitted to paediatric ICU. Oxygen and intravenous fluids were given to all babies. Twenty-two babies had severe respiratory distress, poor perfusion and lactic acidosis. They were given dobutamine at 5 µg/kg/min for 24 hours. Intravenous thiamine 100 mg diluted in 10 mL of normal saline was given as an infusion over 1 hour, once a day for 3 days for all babies.

Serial echocardiography was done at 12 hours, 24 hours and every day until discharge. Follow-up was at 15 days, 1 month, 3 months, 6 months and 12 months. They were followed annually thereafter.

Main outcome measures

Clinical resolution of heart failure and normalisation of PH by echocardiogram were the primary outcomes.

Analysis: mean and SD were used for parametric data. Median and IQR were used for non-parametric data. Frequency table was designed for nominal variables. Box plot was constructed to depict the PASP before and after treatment. CIs were calculated and paired t-test was used as test of significance. A *p* value of <0.01 was considered significant. Statistical software R V.5.2.3 was used for analysis.

RESULTS

A total of 250 infants were recruited in the study (figure 1). Twelve infants did not respond to thiamine. Among 238 infants,

Figure 1 Flow chart of study subjects. PH, Pulmonary hypertension; F/U, follow-up; TRAPH, thiamine-responsive acute pulmonary hypertension.

7 died and 231 showed complete resolution. Data analysis is presented for 238 infants (table 1). The mean age was 3.2 ± 1.2 months. Ratio of male to female was 1.8:1.0 (M=155, F=83). The mean weight was 5.1 ± 0.8 kg and median centile was 19.4 ± 12.3 . Development and immunisation was appropriate for age. Fast breathing and chest retractions were present in all infants. Irritability and poor feeding was found in 87% (208) and vomiting in 50% (119). Hoarseness of voice or aphonia, a characteristic symptom of TRAPH,¹ was found in 40% (96). There was no history of fever or productive cough. Median duration of symptoms was 5 days (range, 1–30). The dietary pattern had common features among all the mothers. Commonly consumed breakfast made of combination of pulses and cereals were not permitted. The diet consisted of polished rice with spicy soup containing very little lentils (*rasam*) for all the three major meals of the day. Other cereals, legumes and animal proteins were taboo. Only few selected vegetables and fruits were permitted.

Table 1 Demographic and clinical profile of children with TRAPH

Gender ratio (male:female)	155:83 (1.8:1)
Age in months (mean±SD) (range)	3.2 ± 1.2 (1–7)
Weight in kg (mean±SD) (range)	5.1 ± 0.8 (3.5–7.6)
Weight centile (mean±SD) (range)	19.4 ± 12.3 (3–61)
Median duration of symptoms in days (range)	5 (1–30)
Median hospital stay in days (range)	4 (1–30)
Median follow-up in months (range)	12 (1–60)
Signs and symptoms	
Fast breathing	238 (100)
Irritability and poor feeding	208 (87)
Vomiting	119 (50)
Aphonia	96 (40)
Tachypnoea/tachycardia/hepatomegaly	238 (100)
Plasma lactate (mmol/L) median (IQR) only for 22 very sick babies	11.6 ± 2.6 (8–15)
Echocardiographic features	
Pulmonary artery systolic pressure at admission (mm Hg) (mean±SD) (range)	73.2 ± 14.4 (50–117)
Pulmonary artery systolic pressure at discharge (mm Hg) (mean±SD) (range)	21.1 ± 6.2 (10–36)
Fall in pulmonary artery systolic pressure after treatment (mm Hg)	52.1 (95% CI 50.2 to 53.9), <i>p</i> <0.01
Patent foramen ovale with right-to-left shunt or bidirectional shunt—n (%)	163 (68)
Tricuspid regurgitation—n (%)	Mild 117 (49) Moderate 93 (39) Severe 28 (12)
Right ventricular dysfunction	148 (62)
TRAPH, thiamine-responsive acute pulmonary hypertension.

Figure 2 Chest X-ray from an infant with thiamine-responsive acute pulmonary hypertension, showing cardiomegaly with dilated right atrium (RA) and pulmonary artery (PA). The lung fields are clear.

Tea or coffee was consumed commonly and milk was rarely consumed. The food restriction was more stringent and lasted for 3 months for male babies and 1 month for females. All patients were belonging to lower socioeconomic class according to Kuppuswamy classification.¹⁰

On examination, all babies were afebrile. They had tachycardia reaching 180 per minute, tachypnoea and hepatomegaly. Hypoxemia with saturations <90% was found in 68% (163). Auscultation revealed clear breath sounds. Loud pulmonary component of second heart sound and tricuspid regurgitation murmur was heard in 46% (111). Chest X-ray showed cardiomegaly with RA and pulmonary artery dilatation (figure 2) in 88% (210) with no lung infiltrates. Blood counts were normal in all except 10 babies who had leucocytosis. Echocardiogram showed dilated RA and RV (figure 3A and video 1). Interventricular septum was bulging towards the left ventricle (figure 3B and video 2). The patent foramen ovale (PFO) showed bidirectional or right-to-left shunt in 68% (163). Moderate or severe TR was found in 46% (111).

Figure 3 Echocardiography in children with thiamine-responsive acute pulmonary hypertension before (A,B) and after thiamine (C,D). (A) Four-chamber view showing dilated RA and RV. (B) Short-axis view showing dilated RV and inter-ventricular septum bulging towards LV. (C) Apical four-chamber view showing normal-sized RA and RV. (D) Short-axis view showing inter-ventricular septum in normal position. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Video 1 Four-chamber view showing dilated RA and RV.

Mean PASP was 73.2 ± 14.4 mmHg (range, 50–117 mmHg). RV dysfunction was found in 62% (148) babies. Left ventricular function was normal in all babies. Thyroid function tests were normal. Twenty-two babies who came in shock had severe lactic acidosis (11.6 ± 2.6 mmol/L) on ABG.

PH completely resolved in 92% (231/250) after thiamine administration. There was acceptance of feeds and cessation of vomiting within 6 hours. Hepatomegaly, tachypnoea and tachycardia reduced within 24 hours. Echocardiogram showed reduction in chamber dimensions (figure 3C,D and video 3), resolution of TR and left-to-right shunting across PFO within 24 to 48 hours. Oxygen saturation normalised. Among the 231 babies, the mean PASP at discharge was 21.1 ± 6.8 mmHg. The mean reduction in PASP from admission to discharge was 52.1 mmHg (95% CI 50.2 to 53.9) (reduction of 71%) with p value of <0.01 (figure 4). Aponia resolved over 3 to 4 ays. Median duration of hospital stay was 4 days (range, 1–30). Two babies became hypoxic and acidotic following a bout of crying and had near cardiac arrest, requiring ventilation and inotropes. With thiamine, they quickly improved, PH resolved and were extubated within 6 hours and discharged by third day.

There were seven deaths (online supplementary table 2). Among them, six babies came in profound shock. All were previously healthy, thriving, exclusively breastfed infants with acute

Video 2 Short-axis view showing dilated RV and inter-ventricular septum bulging towards LV.

Video 3 Apical four-chamber view showing normal-sized RA and RV.

onset of symptoms and similar maternal diets. Echocardiogram showed severe PH with structurally normal heart. Babies were severely acidotic with lactates above 15 mmol/L. Inotropes, thiamine and mechanical ventilation were initiated. Time of survival in the hospital was less than 1 hour. One baby, who was not in overt cardiac failure, had incessant crying during intravenous line insertion. This baby had vomiting and aspiration and could not be resuscitated.

A total of 12 babies did not respond to thiamine (online supplementary table 3). CT scan of chest did not identify any potential pulmonary cause. Associated conditions were small muscular ventricular septal defects in four and mild diaphragmatic eventration in one. Abernethy malformation found in one baby may have contributed to PH. Intrauterine growth restriction was present in two babies. No associations were found in four babies.

Oral thiamine was prescribed at 25 mg for infants and 100 mg for mothers once a day for 3 months. Ten children were lost to follow-up. Ninety-five per cent (221/231) of children were followed up for a maximum of 60 months (1–60 months, median 12, IQR=19). They were symptom free, with normal growth, milestones and echocardiograms. Three children died on follow-up due to unrelated causes.

DISCUSSION

This study describes a large cohort of infants with right heart failure and severe PH. They were all previously well, with normal

Figure 4 Box plot of pulmonary artery systolic pressures before and after treatment with thiamine.

growth. They presented with short duration of fast breathing, vomiting and change in voice. The most common findings were tachycardia, tachypnoea and hepatomegaly. Severe pulmonary hypertension on echocardiography was a universal finding. There was no respiratory or cardiac aetiology that could explain the clinical picture. The response to thiamine administration was dramatic. Resolution of the disease was complete in 92% of the patients within 3 to 4 days. Various studies have used 100 to 150 mg for treatment.^{4 5} We have not found any adverse effects of thiamine at our prescribed doses. High dose of parenteral thiamine has been found to be safe.¹¹ No pulmonary vasodilators were administered other than oxygen. The striking common factors were that they were all exclusively breastfed with a uniform dietary pattern in mothers. The maternal diet consisted of polished rice for all meals with small amount of lentils. No other cereals, pulses or animal proteins were consumed. Most of the commonly consumed vegetables were taboo. Very little or no milk was consumed. All patients were from low socioeconomic strata.

Thiamine deficiency is known to cause severe PH and acute right heart failure. It was described by Albert in 1931.^{12 13} A previously well child presenting with fast breathing, feeding difficulty, tachycardia and hepatomegaly should be suspected to have TRAPH in the relevant geographical and cultural setting. The clinical picture resembles lower respiratory infection or sepsis. Hoarseness or aphonia is not a feature of common paediatric ailments and should alert the physician for possibility of TRAPH.^{2 4 7 13 14} Echocardiogram demonstrates severe PH. There is no demonstrable pulmonary or cardiac cause of PH by chest X-ray or echocardiogram. The diagnosis is based on clinical clues. Lactic acidosis can suggest the possibility of TRAPH.^{6 15} Thiamine should be administered empirically to such infants. Laboratory diagnosis of thiamine deficiency is fraught with many issues. Estimation of serum thiamine reflects recent intake and not functional levels. Low erythrocyte transketolase activity (ETKA) and high thiaminepyrophosphate effect (TPPE) suggest functional thiamine deficiency.^{2 16 17} They are expensive and not routinely available. A 25% increase in ETKA activity (TPPE effect) after addition of thiamine suggests severe deficiency.^{12 17} Response to thiamine administration with resolution of PH is diagnostic.^{2 5 6 18 19} High degree of awareness among paediatricians is required for timely recognition and treatment.

Polished rice is the major dietary component in some states of South India including Karnataka. The outer layer of cereals, legumes, pulses, potato, lean meat, milk and nuts are all rich sources of thiamine.¹ The process of milling, repeated washing, cooking rice in large amounts of water and discarding excess water reduces the vitamin content.¹ The diet in postpartum period is determined by cultural beliefs and taboos. Consumption of polished rice, lack of dietary diversity and food taboos contribute to thiamine deficiency.^{16 20 21}

Thiamine is essential for glucose metabolism and ATP production.¹⁵ Cardiac, central nervous system and skeletal muscles are most affected.^{15 19} Thiamine reduces nitric oxide production and affects vascular resistance and RV filling pressures.^{22 23} Deficiency leads to high flow states. High flow causes shear stress on pulmonary endothelium releasing vasoconstrictor substances resulting in PH. Right-to-left shunting across the PFO causes hypoxemia. Crying probably causes a sudden surge in PH with acute drop in cardiac output as seen in our subjects. Administration of thiamine restores the vascular tone, and normalises the cardiac output and filling pressures.²³ High flow states like hyperthyroidism or AV fistulas can cause severe pulmonary hypertension.^{24 25} Aphonia is postulated to be due to palsy of

Table 2 Thiamine deficiency in infants—historical evidence

Period	Geographical area	Type of report	Numbers	Authors
1987–1990	Thailand—Karen refugees	Infant mortality	183 per 1000 to 78 per 1000	Luxemburger <i>et al</i> ¹⁸
1906–1930	Manila	Infant mortality rate	476.17 to 160.24	Albert ¹²
1931	Philippines	Infant mortality in the community	12 000 to 20 000 infant deaths due to beriberi	Report of League of Nations ²⁷
1931	Philippines	Case series	514 infants	Albert ¹³
1936	Singapore	Case series	139 infants/77 deaths	Haridas ²⁸
1954–1958	Philippines		15 200 infant deaths	Williams ²⁹
2005	Israel	Case series	8 infants	Fattal-Valevski <i>et al</i> ³⁰
2007–2009	Laos, Thailand	Case series	85 infants approximately/20 deaths	Barennes <i>et al</i> ⁷
2010	Southern India (Hyderabad)	Case series	55 infants	Rao and Chandak ⁴
2016	Northern India (Kashmir)	Case series	29 infants/4 deaths	Bhat <i>et al</i> ⁵
2017	India (Kashmir)	Case series	23 infants	Qureshi <i>et al</i> ⁶

recurrent laryngeal nerve caused by compression from dilated pulmonary artery or by direct involvement.¹⁴

The historical perspective of infantile beriberi is presented in table 2. The largest numbers of infantile beriberi were described from Philippines during the period from 1906 to 1930, 1954–1958 and again in 2007.⁷ Infant mortality rates decreased from 476.1 to 160.2 per 1000 live births after supplementation with rice polish extract.¹² To the best of our knowledge, the present study is probably the largest published after the year 1960. Echocardiographic documentation of PH and rapid reversal with thiamine has been shown in a large group of infants. A population with a high infant mortality, especially a second peak between 1 and 6 months of life, is an epidemiological sentinel for infantile beriberi.^{3–6 16 18}

TRAPH seen here is the most severe manifestation. There is likely to be subclinical deficiency in the population which far exceeds in magnitude. This bears a significant impact on public health. Meticulous analysis of the nutrition content of the cereals and pulses provided in the public distribution system and appropriate rectification measures will have a larger impact on thiamine status of the community.²³ Study of cultural practices, food taboos and education of the community is an essential and uphill task in the long run.^{20 21} Alternate methods of food processing like hand milling and par boiling, food fortification of wheat flour, rice and fish paste have improved thiamine status of community.²³ Thiamine supplementation to pregnant and postpartum mothers and infants is followed in Myanmar to combat thiamine deficiency.¹³ The entity of TRAPH is not included in sixth World Symposium on Pulmonary Hypertension classification of paediatric PH²⁶ indicating lack of global awareness.

Limitations of the study

Laboratory testing for thiamine levels as an objective proof of deficiency was not possible. We firmly believe that dramatic therapeutic response is fairly diagnostic of thiamine deficiency. 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.

CONCLUSIONS

TRAPH presents as acute onset of respiratory distress, vomiting and aphonia in a previously well exclusively breastfeeding infant. Examination shows tachycardia, tachypnoea and hepatomegaly. Echocardiography shows severe PH. Administration of thiamine leads to rapid improvement within 48 hours. Delayed treatment can be fatal. Diet and cultural practices are contributing factors.

A high level of clinical suspicion is required to recognise this easily treatable but fatal disease.

Contributors UMKS conceptualised the study, drafted the protocol and was primarily responsible for data acquisition and drafting the manuscript, analysis and interpretation of data. JM, BAP, AS, AM: conception of the study design, drafting the protocol, data compilation, suggestions, reviewed and revised the manuscript. RKK: scientific review, critical analysis and manuscript editing. SG: statistical analysis and interpretation of data, critical review of the manuscript for intellectual content. MG: designing the protocol, assistance in drafting the manuscript, compiling references, editing the manuscript and critical suggestions. CNM: conception of study design and protocol, supervision of the study, final approval of the submission version. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. Dr Nisha C Babu and Dr Ravishankar: assistance in data acquisition.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval Institutional ethics committee approval was obtained. Parents gave informed consent for the study. Ethics Committee clearance obtained: Sri Jayadeva Ethics Committee: 25 Jan 2013.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplementary information. Individual participant data that underlie the results will be available after deidentification 1 year after the publication of the article to those researchers who submit a methodologically sound proposal for the purpose of meta-analysis. Data will be available on requesting the corresponding author (docmkusha@gmail.com).

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