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Infantile thiamine deficiency: Redefining the clinical patterns

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Objectives: Thiamine deficiency (TD) is frequently suspected and treated at our hospital. In our retrospective study, we aimed at finding the clinical and laboratory spectrum of infantile TD presenting to a single center over a period of time.
Methods: The diagnosis was made on criterion standard of response to thiamine challenge.
Results: TD was suspected in 189 infants at admission; 43 infants were diagnosed as having TD in three distinct forms and a fourth group with mixed presentation. The first group (n = 30), which was the youngest (mean age = 67 d), was always associated with lactic acidosis. They had history of reflux and suddenly became irritable and developed acidotic breathing. This further worsened into shock (46%) and acute respiratory failure (50%). The second group (n = 5) presented with pulmonary arterial hypertension. They had hoarseness of voice and irritability. Chest radiograph showed prominent pulmonary conus. Their clinical course was complicated by congestive heart failure in three. Echocardiographic response to thiamine was uniformly seen within 3 d in this group. The clinical presentation of infants with Wernicke's encephalopathy (n = 5) who were the oldest of all (mean age = 190 d) was constantly marked by presence of bilateral ptosis and encephalopathy preceded by occurrence of vomiting. Their head ultrasonography showed presence of hyperechoic basal ganglia.
Conclusions: Three clinically distinct forms of TD were recognized. Lactic acidosis was a universal finding in acidotic form. Infants with pulmonary hypertension as primary presentation are typically associated with aphonia. Infants with Wernicke's encephalopathy can be clinically diagnosed by presence of encephalopathy and ophthalmic signs (ptosis).

Introduction

The staple diet of Kashmir region is polished rice. Polished rice is a poor source of thiamine. It is high in carbohydrate content resulting in thiamine calorie imbalance [1]. Repetitive rice washing, cooking, discarding of cooking water, a restrictive postpartum diet because of cultural habits, and ingestion of antithiamine factors (e.g., tea) further increases the risk of thiamine deficiency (TD) [2–4]. Exclusively breast fed infants of thiamine-deficient mothers are at highest risk [1].

Utilization of thiamine depends on glucose utilization and expression of thiamine transporters in that organ. This explains the multiple and organ-specific (e.g., nervous and cardiac) involvement in TD.

Adults can have varied presentations of TD. Classically they have either a neuritic form, which usually affects the peripheral nerves and presents as neuropathy, or a cardiologic form, which primarily affects heart and blood vessels. Sometimes there can be a mixed presentation [1]. The commonest from of TD in adults is seen in persons with alcoholism and presents in the form of Wernicke Korsakoff psychosis or encephalopathy [5]. Peripheral neuropathy due to TD has also been documented [6]. It can follow gastrectomy [7]. Manifestations of TD can be precipitated in pregnancy [8]. In addition to those listed above, TD can have myriad of other neurologic and psychiatric manifestations [9].

In infants, the clinical spectrum of acute TD disorders includes cardiologic form, aphonic form, pseudomeningitic form, and Wernicke's encephalopathy (WE) [1]. Shoshin beriberi, is a fulminant cardiologic form marked by acute cardiogenic shock, multiorgan failure, no edema, and type B lactic acidosis [10]. Pulmonary hypertension has been found in infants with cardiogenic shock and congestive heart failure on echocardiography [11]. Infants have a truncated form of WE without ataxia [12].

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Analysis of thiamine diphosphate in whole blood or erythrocytes is a useful biomarker of thiamine status because it is reflective of body stores. However, thiamine diphosphate levels do not assess thiamine metabolic function. Erythrocyte transketolase activity demonstrates the functionality of the vitamin, but the assay is not widely available. The criterion standard diagnostic test of beriberi is rapid clinical response to thiamine [13]. TD is underdiagnosed as a result of lack of clinical awareness, as a result of the wide spectrum of presentations, and because the illness mimics many commonly occurring infantile conditions. Therefore, a large number of infants are deprived of therapeutic thiamine challenge as a means to prevent fatal consequences or permanent neurologic sequelae.

Given the reports of beriberi in Kashmir valley, TD is frequently suspected and treated at our hospital. We hereby describe the clinical phenotypes and laboratory findings of acute TD in infants presenting in our hospital.

Materials and methods

Retrospective review of medical records of infants from the period of January 2016 to December 2016 was carried out in the Department of Pediatrics at GB Pant Hospital, a tertiary care referral hospital at Srinagar, Union territory of Jammu and Kashmir, India. The study was done after institutional ethical approval.

All infants from the age of 1 mo onward in whom parenteral thiamine was given at admission were eligible for the study. Infants were divided into two groups: (1) those given final diagnosis of infantile TD and (2) those who had a final diagnosis other than infantile TD. The diagnosis of TD had been made by rapid response to thiamine and after exclusion of relevant differential diagnosis. In the following groups of infants, diagnosis other than TD had to be made, although thiamine had been given at admission:

- infants in whom lactic acidosis was explained by shock due to sepsis, metabolic disorders, and hypoxemic states;
- infants in whom encephalopathy was explained by hypoglycemia, seizures, inborn metabolic errors, sepsis, and meningoencephalitis; and
- infants with congenital heart disease, chronic lung disease, dysmorphism, and suspected genetic disorders that had resulted in pulmonary hypertension.

Infants were diagnosed to be in encephalopathy if they had presence of two of the following symptoms: altered state of consciousness, seizures, and altered personality or cognition. For diagnosis of WE, presence of ophthalmoplegia or nystagmus and altered sensorium were required. Severe metabolic acidosis was defined as blood pH of less than 7.2. Lactic acidosis was defined as blood lactate levels more than 4 mmol/L. Pulmonary arterial hypertension had been defined as per 2015 European society of cardiology guidelines for high probability of pulmonary arterial hypertension (PAH) by echocardiography [14].

Data regarding the following variables was retrieved from the case records and analyzed: Demography, symptoms, recent immunization history, significant perinatal and past history, consanguinity, significant obstetric history, sibling deaths, dietary history, examination findings, treatment received in the hospital, and hospital course (time taken to respond to treatment, time of stay, and any complications encountered during hospital stay).

Patients had been investigated as per standard protocol to look for the etiologies. This included complete blood count, blood culture, urine examination, serum biochemistry, electrolytes, blood sugar, lactate, blood gases, tandem mass spectrometry, and urine gas chromatography mass spectrometry in infants who had presented with acidotic breathing. Head ultrasonography had been performed in infants who presented with encephalopathy. Cerebrospinal fluid examination, computed tomography scan of the head, and head magnetic resonance imaging (MRI) had been performed at the discretion of the treating physician in such patients. Two-dimensional echocardiography had been used to diagnose pulmonary arterial hypertension. Repeat echocardiography for reassessment of pulmonary pressures had been done within the hospital stay. Data regarding the aforementioned investigations were also retrieved from the case records and analyzed.

Statistical analysis

The data were summarized and presented in form of numbers and percentages. Mean and SD were used to summarize continuous variables.

Results

During the year of 2016, a total of 189 infants were given thiamine at admission. However, only 43 infants had a discharge diagnosis of infantile TD. Almost half of them were admitted in summer and autumn. All infants were premorbidly well. There was rural predominance (29:14). No infant had failure to thrive.

The majority of infants had an acidotic presentation with biochemical evidence of lactic acidosis. These infants had a lower mean age; 67 d (range, 30–180 d). They had presented in the emergency department with acidotic or fast breathing with moaning sounds preceded by vomiting and irritability. Metabolic acidosis was severe and caused by excessive lactate. The mean pH at admission was 7.13. Six infants had pH $<$ 7.0. However, two had pH $>$ 7.36. Blood lactate ranged from 5 to $>$15 mmol/L. 15 mmol/L was the upper limit of detection on the analyser. Bicarbonate infusion was given when acidosis was severe. Lactate was normalized within 8 h. Tachycardia was almost universal. Nearly half of the infants had presented in shock with poor perfusion and unrecordable blood pressure. Reversal of shock was achieved within 1 h and required slow saline boluses and in some cases pressor support. None of the infants had edema. Seven infants were either admitted in gasping state or started gasping while being cannulated. One-third of infants had acute symptomatic seizures during or before hospitalization. Witnessed seizures were marked by tonic posturing and retrocollis and required anticonvulsants for seizure control. Half of the infants needed brief periods of ventilation (2–72 h). Random blood sugars were $>$250 mg/dL at admission in six babies. In three infants vaccination with a liquid pentavalent vaccine containing diptheria, whole-cell pertusis, tetanus, hemophilus and hepatitis B was noticed as a trigger. One infant had been circumcised a week before illness. There were sudden sibling deaths in two infants with similar presentation. The echocardiographic examination done only (in nine infants) after infants were stabilized was normal. Head ultrasonographies done in 15 infants were positive for hyperechoic basal ganglia in three infants. Computed tomography scan of head done in two confirmed the same findings in one. The mean hospital stay was 7 d (range, 2–17 d). Breastfeeding was reestablished within 1 d.

Table 1 depicts clinical features, laboratory parameters, and complications of patients who presented with lactic acidosis.

Five infants had presented with signs and symptoms of pulmonary arterial hypertension. Their mean age was 158 d (range, 52–330 d). The presentation was marked by hoarseness of voice and irritability. Signs of PAH and tachycardia were evident on cardiovascular examination. PAH was complicated by right heart failure (in three) and shock (in one). There was no other organ injury. Chest radiography showed prominence of pulmonary conus. The mean pulmonary pressure was 52 mm Hg. The right atrium and right ventricle were dilated, and there was right ventricular systolic and diastolic dysfunction. Normalization of pulmonary arterial pressures and marked improvement in right ventricular systolic and diastolic dysfunction and dimensions were achieved within 72 h (mean) of hospitalization. Mean probrain natriuretic peptide levels measured in three infants were high (19 700 ng/mL). Their mean blood pH and lactate was 7.26 and 5.62, respectively. Mean hospital stay was 4 d (range, 2–6 d). No triggers were established on history.

Table 2 depicts clinical features, laboratory parameters, and complications of patients who presented with pulmonary arterial hypertension.

Clinical phenotype of WE was obvious in five infants. Their mean age of presentation was 190 d (range, 160–240 d). The prototype was an infant more than 6 mo of age not yet started on complementary diet who presented with history of vomiting for few days followed by bilateral ptosis, vacant stare, and encephalopathy. All infants were verbal on AVPU (alert, response to verbal, painful stimuli, unresponsive) scale. Response to thiamine was evident with ptosis resolving in 6 h and encephalopathy in 12 h. Three infants

Table 1
Clinical features, laboratory parameters, and complications of patients with lactic acidosis

Clinical features	n (%)
Systemic	
Fever	4 (13)
Vomiting	10 (33)
Diarrhea	1 (3)
Decreased feeding	7 (23)
Respiratory	
Cough	7 (23)
Fast/acidotic breathing	12 (39)
Gasping	7 (23)
CVS	
Tachycardia	24 (80)
Shock	14 (46)
CNS	
Irritability	16 (53)
Lethargy	4 (13)
Moaning	15 (50)
Seizure/seizure equivalent	11 (36)
Laboratory parameter	Mean ± SD (normal range)
Hb (g/dL)	10.3 ± 1.35 (9.5–13.5)
TLC (× 1000/mm^3)	11.7 ± 5.21 (9.1–14.5)
Platelet count (10^5/mm^3)	4.4 ± 1.5 (1.5–4.5)
Serum urea (mg/dL)	21.3 ± 9.85 (8–28)
Serum creatinine (mg/dL)	0.6 ± 1.6 (0.12 –1.06)
Serum ALT (U/L)	30 ± 19.62 (6–50)
Serum AST (U/L)	45 ± 39.51 (20–60)
Plasma albumin (g/dL)	3.6 ± 0.4 (2.8–5.0)
Serum sodium (mEq/L)	137.7 ± 9.7 (133–145)
Serum potassium (mEq/L)	4.3 ± 0.9 (4.0–5.5)
Blood pH	7.13 ± 0.24 (7.34–7.46)
HCO_3 (mEq/L)	10.1 ± 4.21 (23–30)
pCO_2 (mm Hg)	28.8 ± 11.78 (26–41)
Base exchange	−16.7 ± 5.69 (−5 to 3)
Lactate (mmol/L) (range)	5 to > 15 (0.2–2)
Complications	n (%)
Acute respiratory failure	15 (50)
Cardiogenic shock	14 (46)
Severe metabolic acidosis	11(36)
Seizures	11(36)

ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; CNS, central nervous system; CVS, cardiovascular system; Hb, hemoglobin; pCO_2, partial pressure of carbon dioxide; TLC, total leucocyte count.

Table 2
Clinical features, laboratory parameters, and complications of patients with pulmonary hypertension

Clinical features	n (%)
Systemic	
Decreased feeding	1 (20)
Respiratory	
Hoarseness of voice	3 (60)
Cough	1 (20)
Fast breathing	2 (40)
CVS	
Tachycardia	4 (80)
Shock (poor perfusion/low BP)	1 (20)
Loud P2	3 (60)
TR murmur	1 (20)
CNS	
Irritability	2 (40)
Lethargy	1 (20)
Seizure/seizure equivalent	1 (20)
Abdomen hepatomegaly	3 (60)
Laboratory parameter	Mean ± SD (normal range)
Hb (g/dL)	10.1 ± 0.67 (9.5–13.5)
TLC (× 1000/mm^3)	9.7 ± 2.31 (9.1–14.5)
Platelet count (10^5/mm^3)	345 ± 23 (1.5–4.5)
Serum urea (mg/dL)	23 ± 7 (8–28)
Serum creatinine (mg/dL)	0.5 ± 0.1 (0.12–1.06)
Serum ALT (U/L)	40 ± 7.1 (6–50)
Serum AST (U/L)	40 ± 14.2 (20–60)
Plasma albumin (g/dL)	3.8 ± 0.2 (2.8–5.0)
Serum sodium (mEq/L)	145 ± 3.1 (133–145)
Serum potassium (mEq/L)	3.7 ± 0.2 (4.0–5.5)
Blood pH	7.26 ± 0.23 (7.34–7.46)
HCO_3 (mEq/L)	17 ± 2.7 (23–30)
pCO_2 (mm Hg)	32 ± 3.51 (26–41)
Base exchange	−9.4 ± 1.88 (−5 to 3)
Lactate (mmol/L)	5.62 ± 2.79 (0.2–2)
Complications	n (%)
Acute respiratory failure	0
Cardiogenic shock	1 (20)
Severe metabolic acidosis	1 (20)
Seizures	1 (20)
Right heart failure	3 (60)

ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; BP, blood pressure; CNS, central nervous system; CVS, cardiovascular system; Hb, hemoglobin; pCO_2, partial pressure of carbon dioxide; SD, standard deviation; TLC, total leucocyte count; TR, tricuspid regurgitation.

developed seizures, which were treated with anticonvulsants for a brief period. Mean blood pH and lactate was 7.35 and 4.2, respectively. All of the five infants had hyperechoic basal ganglia on head ultrasonography. Mean hospital stay was 3 d (range, 2–6 d).

Table 3 depicts clinical features, laboratory parameters, and complications of patients who presented with WE.

Three infants had a mixed presentation. Of them one was 60 d old who had both signs of WE and PAH. His blood pH and lactate were normal. He required invasive ventilation. The second was 6 mo old who presented with acidotic breathing and signs of PAH. He required bicarbonate, invasive ventilation and needed pressors for shock. The third infant was 90 d old who had clinical signs of WE and acidotic breathing. He also received bicarbonate.

All infants with TD were exclusively breastfed. There were no obvious clinical signs of TD in mothers.

In 146 infants given thiamine, diagnosis other than infantile TD was reached as depicted in Table 4. The commonest illness with which infantile TD was confused was bronchiolitis. The other common diseases where infantile TD was thought of as an admission diagnosis were pneumonia and gastrointestinal diseases (acute gastroenteritis, gastroesophageal reflux, infantile colic). Seventeen infants with seizures were also given thiamine at admission.

Discussion

As the global nutrition improved, TD was thought to have vanished. However, the disease reemerged as many conflicts across the world caused human displacement, giving rise to a large number of refugee populations who did not have access to adequate nutrition [15]. Similarly, the advent of mechanized milling of rice thereby removing the thiamine-rich layer of the rice grain put those populations at risk of TD who are dependent on rice as a major staple food [16]. Infantile TD has gone hand in hand with adult TD. It has been shown to be responsible for a large scale early infantile mortality among thiamine-deficient populations. Thiamine-deficient mothers produce breastmilk poor in thiamine, which is responsible for TD in their breastfed babies [17]. We faced a similar situation where a large number of infants died because of apparently unidentified cause. Later on after thiamine was instituted as primary therapy in these children, patient mortality due to this disease has reduced. Typical dietary practices, milled white rice as a staple food, and customary dietary practices during lactation and pregnancy have been identified as possible risk factors for TD in this part of the world [18]. Typically severe metabolic acidosis, severe pulmonary

Table 3
Clinical features, laboratory parameters, and complications of patients with Wernicke's encephalopathy

Clinical features	n (%)
Systemic	
Fever	1 (20)
Vomiting	3 (60)
CNS	
Low GCS	5 (100)
Seizure/seizure equivalent	3 (60)
Respiratory	
Cough	1 (20)
Ophthalmologic	
Vacant stare	5 (100)
Ptosis	5 (100)
Divergent squint	2 (40)
Laboratory parameter	Mean ± SD (range)
Hb (g/dL)	10 ± 0.38 (9.5–13.5)
TLC (× 1000/mm^3)	10.6 ± 0.89 (9.1 –14.5)
Platelet count (10^5/mm^3)	271 ± 40.2 (1.5–4.5)
Serum urea (mg/dL)	14 ± 3.4 (8–28)
Serum creatinine (mg/dL)	0.46 ± 0.08 (0.12–1.06)
Serum ALT (U/L)	39 ± 6.51 (6–50)
Serum AST (U/L)	36 ± 7.28 (20–60)
Plasma albumin (g/dL)	3.8 ± 0.45 (2.8–5.0)
Serum sodium (mEq/L)	138 ± 6.1 (133–145)
Serum potassium (mEq/L)	3.8 ± 0.2 (4.0–5.5)
Blood pH	7.35 ± 0.26 (7.34–7.46)
HCO_3 (mEq/L)	17 ± 2.34 (23–30)
pCO_2 (mm Hg)	38 ± 3.5 (26–41)
Base exchange	4.7 ± 0.49 (–5 to 3)
Lactate (mmol/L)	4.2 ± 0.82 (0. –2)
Complications	n (%)
Acute respiratory failure	0
Cardiogenic shock	0
Life-threatening acidosis	0
Seizures	3 (60)
AVPU-V	5 (100)

ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; AVPU, alert, response to verbal, painful stimuli, unresponsive; CNS, central nervous system; GCS, Glasgow Coma Scale; Hb, hemoglobin; pCO_2, partial pressure of carbon dioxide; SD, standard deviation; TLC, total leucocyte count.

Table 4
Infants with diagnosis other than infantile TD given thiamine

Diagnosis	n (%)
Respiratory	
Bronchiolitis	26 (18)
Pneumonia	25 (17)
Pertussis	2 (1)
Cardiovascular	
Congenital heart disease	3 (2)
Kawasaki	1 (0.6)
Central nervous system	
Seizures	17 (11)
Meningitis/meningoencephalitis	6 (4)
Gastrointestinal	
Acute gastroenteritis	11 (7.5)
Gastroesophageal reflux	9 (6)
Infantile colic	7 (5)
Intussusception	2 (1)
Other infections	
Urinary tract infections	3 (2)
Sepsis	4 (3)
Adverse events after immunization	7 (5)
Hematologic	
Severe anemia	1 (0.6)
Renal	
Renal tubular acidosis	3 (2)
Nonspecific	
Irritability	15 (10)
Fever	4 (3)

TD, thiamine deficiency.

artery hypertension, and WE have been reported from various centers in this region [19–21]. In our present study, we aimed at finding the clinical and laboratory spectrum of TD presenting to a single center over a period of time. This has not been attempted earlier, and all the studies previously have described various presentations in isolation.

The diagnosis of TD in our study was made by a rapid reversal of clinical signs, symptoms, and laboratory parameters after administration of parenteral thiamine. Although there are many objective tests to determine thiamine status, these are not easily available or affordable. Because response to parenteral thiamine is rapid and can be objectively judged on the basis of improvement in clinical signs, symptoms, and laboratory parameters, it can be and has been conventionally used as a criterion standard in the diagnosis of functional TD [10].

This study has been able to identify three clinically identifiable forms of TD and a fourth group that had mixed features of the three forms. Of 189 infants given thiamine challenge at admission, in 146 infants, TD was excluded after complete work-up (Fig. 1). It underscores the fact that TD in endemic areas remains one of the working diagnoses at admission for illnesses with similar symptoms. The lack of diagnostic facilities justifies the use of giving thiamine challenge given that potential for benefit is huge and likelihood of toxicity is very negligible [22].

The first and the major group encountered was acidotic form. We refer to this group as acidotic because lactic acidosis was universal in these patients. These infants were typically premorbidly normal. They presented only after a mean age of 1 mo. Given the inability of humans to synthesize thiamine and its limited body storage, the time taken for clinical deficiency to manifest is as early as 2 wk in absence of replacement. This age of presentation therefore can be explained by insufficient thiamine in breast milk. However, thiamine content of breast milk was not measured. Vaccination with diphtheria, whole-cell pertussis, and tetanus causes local inflammation and might therefore act as a thiamine-consuming trigger. These observations are well known [1].

The acidotic presentation marked by vomiting, irritability, moaning, and tachycardia was explainable by lactic acidosis. High lactate levels were constant and observed even in infants with no acidosis. Shock was present in only half. We concluded that lactic acidosis was not a result of shock. Biologically active form of thiamine is a cofactor of enzyme pyruvate dehydrogenase complex, which converts pyruvate to acetyl coenzyme A; the precursor to the Krebs cycle. Deficiency of thiamine therefore results in accumulation of pyruvate and its conversion to lactate by anerobic glycolysis. Presence of shock could have contributed to high lactate. Shock was cardiogenic, likely because of TD in the myocardium and severe metabolic acidosis. Potassium was normal because metabolic acidosis was organic. High sugars were observed in six babies, likely because of stress release of glucocorticoids.

Sibling deaths in two of these patients because of similar looking illness are consistent with TD. Sibling deaths are explained because similar nutrition is shared among the siblings and possibly unrecognized TD was the cause of death in previous siblings. Sudden infant death syndrome and sudden unexplained nocturnal death syndrome have been reported previously with TD [23].

Findings of hyperechoic basal ganglia were seen in 20% of these infants on head ultrasonography, confirming earlier observation by Wani et al. [24] that this finding is less often seen in acidotic form of TD. Unfortunately because of lack of bedside echocardiography facilities, echocardiography was delayed in this group of patients and done only after patients were out of crisis after being given thiamine treatment. Therefore presence of pulmonary hypertension at admission could not be ruled out.

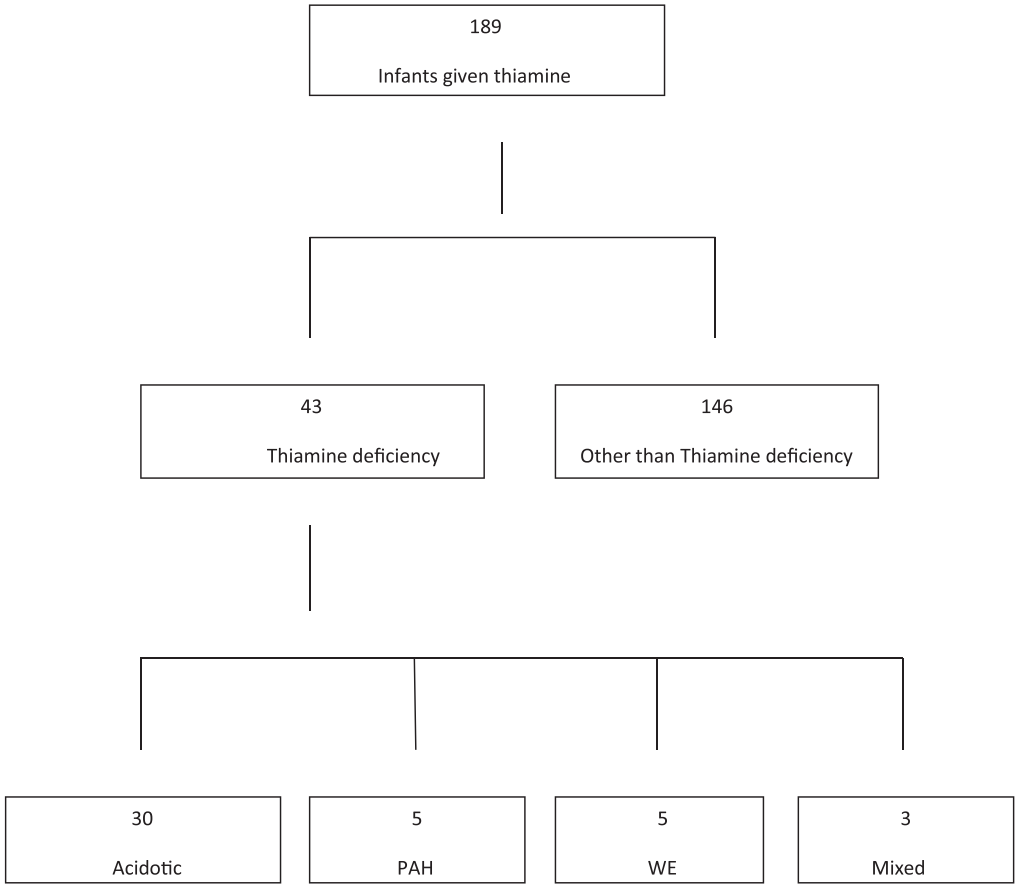

Fig. 1. Breakdown of infants given thiamine. The diagnosis of 146 infants with "other than infantile TD" is given in Table 4. PAH, pulmonary arterial hypertension; TD, thiamine deficiency; WE, Wernicke's encephalopathy.

The presentation of this group resembled that of cardiologic form originally described by the World Health Organization, with sicker infants having Shoshin beriberi, a fulminant variant of wet beriberi, which is characterized by acute cardiogenic shock with lactic acidosis, multiorgan failure, and no edema [10]. We believe that the cardiologic form of beriberi is actually the acidotic form.

Given the constant finding of lactic acidosis, the authors recommend giving an empirical trial with thiamine in all exclusively breastfed infants of this age group with lactic acidosis who have the nonspecific signs and symptoms as described.

The signs and symptoms of sudden-onset irritability and vomiting complicated by acidosis and shock in a previously well baby suggest a differential diagnosis of sepsis or metabolic disorder, such as organic acidemia, but with negative sepsis markers, cultures, and tandem mass spectrometry and urine gas chromatography mass spectrometry these could be excluded.

Infants with PAH as a primary presentation presented at a mean age of 5 mo with nonspecific symptoms or right heart failure. Contrary to findings of Bhat et al. [20] we did not observe any evidence of biventricular failure or acute liver or kidney injury in infants with pulmonary hypertension. An interesting finding of aphonia in PAH was observed. This is postulated to be because of recurrent laryngeal nerve palsy by local nerve damage and laryngeal edema secondary to right heart failure. Sebrel (1962) [32]originally described aphonic form of infantile beriberi in the age group of 4 to 6 mo. However, no echocardiographies were done. We found that aphonic form of beriberi is associated with PAH; however, not all infants with PAH had aphonia. The study by Rao et al. [11] found aphonia in 18% of children with cardiac beriberi (10 of 55), who had high output cardiac failure and evidence of pulmonary hypertension. Bhat et al. [25] described aphonia in 8% of children (4 of 50) presenting as "encephalopathy" owing to TD. We did not find aphonia in any of our patients with acidotic or WE form of TD. Based on our observations we would suggest infants of this age group with aphonia without any other signs of upper respiratory illnesses be screened for PAH in endemic areas.

Acidosis can precipitate pulmonary hypertension, but we did not observe severe metabolic acidosis in all patients with pulmonary hypertension. This study has left little doubt that TD causes raised pulmonary pressures in a proportion of these infants, but the actual pathophysiology is not clear yet. The response of PAH to thiamine was quick and occurred within 3 d.

WE as a manifestation of TD is not limited to adults. Infants develop a modified form of WE without ataxia. The characteristic clinical presentation of bilateral ptosis, vacant stare, and encephalopathy preceded by vomiting in this group of infants resembled an epidemic in southern India at Hyderabad [26]. However, we did not observe breathing difficulties in these children, probably because they reported and were treated earlier. In the study of Bhat et al. [25] 60% of infants with acute onset infantile encephalopathy due to infantile TD had blepharoptosis. The mean age of presentation of WE was in later part of early infancy. The dietary history was characteristically marked by absence of addition of complementary diet in those who reported at age more than 6 mo. The mean blood lactate was almost normal because lactate accumulation in WE occurs initially in cerebrospinal fluid and brain. This is revealed on

magnetic resonance spectroscopy as a lactate doublet peak. Head ultrasonography images in all infants with WE demonstrated hyperechoic basal ganglia (with characteristic pattern of putamen involvement in all, caudate involvement in 4, and thalamic involvement in 1). Wani et al. [24] had earlier observed that clinical presentation was an independent risk factor for positive findings of hyperechoic basal ganglia on cranial ultrasonography. They found that sensitivity of head ultrasonography in WE and acidotic forms was 90% and 43%, respectively. However, our study was not designed to study actual sensitivity and specificity of head ultrasonography in TD. Imaging with MRI was not done, which would have delineated cortex and brain stem better but would not have changed the treatment. In their investigation of brain MRI in infants with WE Kornreich et al. [27] found that TD is characterized by involvement of frontal lobe and basal ganglia in addition to lesions in periaqueductal region, thalami, and mammillary bodies described in adults. Findings of Wani et al. [28] and Rao et al. [26] have earlier described universal involvement of putamen in Indian population, a finding different from that of Israeli children fed on thiamine-deficient formula [29]. Multiple mechanisms (altered oxidative carbohydrate metabolism with inadequate adenosine triphosphate production and lactic acidosis, reduced antioxidant production with neuronal cell death, alteration in levels of neurotransmitters with excessive glutamate induced neurotoxicity) have been implicated in neuronal injury [30,31].

The basal ganglia are rich in mitochondria and vascular supply, making them vulnerable. Acute Leigh disease being an important differential diagnosis has overlapping clinical and radiologic features with WE because of common pathophysiology of mitochondrial damage. However, it is marked by progressive neurologic symptoms with episodic symptomatic exacerbations.

The fact that three infants had mixed presentations suggests that there are grey areas, and symptoms from different phenotypes may be present in the same patient. In describing cardiologic form of beriberi Rao et al. [20] reported that 4 of 55 patients with wet beriberi had WE.

The limitations of this study were that it relied on secondary data, outpatients given thiamine were not part of the study, infants who may have died of TD were not part of study, and concomitant low thiamine levels in those who had diseases other than TD could not be ruled out.

Conclusions

In conclusion, this study clearly describes three clinically distinct forms of TD. Lactic acidosis was a universal finding in acidotic form. Infants with “cardiologic form” described by WHO have evident acidosis. Infants with pulmonary hypertension as primary presentation are typically associated with aphonia, with prominent pulmonary conus on chest radiographs. “Aphonic form” described by WHO seems to be the PAH form of TD. Infants with WE can be clinically diagnosed as having altered sensorium and ophthalmic signs (ptosis) at presentation. Presence of hyperechoic basal ganglia on ultrasonography will confirm the diagnosis. Some children had mixed presentations. No pseudomeningitic form was identified in our cohort. A distinct encephalopathic form was also not identified. However, many infants with all the three forms including acidotic and PAH were in encephalopathy explainable by severe metabolic acidosis, shock, and respiratory failure. Encephalopathy in WE was because of primary involvement of the brain. Blood gas analysis with lactate, bedside echocardiography, and screening head ultrasonography can identify most of the cases of TD in this part of the world.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2020.111097.

References

[1] World Health Organization. Thiamine deficiency and its prevention and control in major emergencies. Geneva, Switzerland: Department of Nutrition for Health and Development, World Health Organization; 1999.
[2] Yagi N, Itokawa Y. Cleavage of thiamine by chlorine in tap water. J Nutr Sci Vitaminol (Tokyo) 1979;25:281–7.
[3] Liu K, Zheng J, Wang X, Chen F. Effects of household cooking processes on mineral, vitamin B, and phytic acid contents and mineral bioaccessibility in rice. Food Chem 2019;280:59–64.
[4] Hilker DM, Somogyi JC. Antithiamins of plant origin: their chemical nature and mode of action. Ann N Y Acad Sci 1982;378:137–45.
[5] Isenberg-Grzeda E, Kutner HE, Nicolson SE. Wernicke-Korsakoff-syndrome: under-recognized and under-treated. Psychosomatics 2012;53:507–16.
[6] Koike H, Iijima M, Sugiura M, et al. Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. Ann Neurol 2003;54:19–29.
[7] Koike H, Iijima M, Mori K, et al. Postgastrectomy polyneuropathy with thiamine deficiency is identical to beriberi neuropathy. Nutrition 2004;20:961–6.
[8] Oudman E, Wijnia JW, Oey M, van Dam M, Painter RC, Postma A. Wernicke's encephalopathy in hyperemesis gravidarum: a systematic review. Eur J Obstet Gynecol Reprod Biol 2019;236:84–93.
[9] Dhir S, Tarasenko M, Napoli E, Giulivi C. Neurological, psychiatric, and biochemical aspects of thiamine deficiency in children and adults. Front Psychiatry 2019;10:207.
[10] Whitfield KC, Bourassa MW, Adamolku B, et al. Thiamine deficiency disorders: diagnosis, prevalence and a roadmap for global control programs. Ann N Y Acad Sci 2018;1430:3–43.
[11] Rao SN, Chandak GR. Cardiac beriberi: often a missed diagnosis. J Trop Pediatr 2010;56:284–5.
[12] Hiffler L, Rakotoambinina B, Lafferty N, et al. Thiamine deficiency in tropical pediatrics: new insights into a neglected but vital metabolic challenge. Front Nutr 2016;3:16.
[13] Gomes F, Bergeron G, Bourassa M. National control and prevention programs for thiamine deficiency disorders. Technical reference materials. New York: The New York Academy of Sciences; 2019.
[14] Galie N, Humbert M, Vachiery J, et al. 2015 ESC/ERF diagnosis and treatment of pulmonary hypertension. Eur Respir J 2015;46:903–75.
[15] Luxemburger C, White NJ, Kuile F, et al. Beriberi: the major cause of infant mortality in Karen refugees. Trans R Soc Trop Med Hyg 2003;97:251–5.
[16] Sonata Green. SUGAWA embryo rice machine. Available at: https://sonata-green.com/en/products/kitchen-series/embryo-rice-machine. Accessed July 10, 2019.
[17] Allen LH. B vitamins in breast milk; relative importance of maternal status and intake, and effects on infant status and function. Adv Nutr 2012;3:362–9.
[18] Shah IA, Asimi RP, Kawoos Y, et al. Nonalcoholic Wernicke's encephalopathy: a retrospective study from a tertiary care center in Northern India. J Neurosci Rural Pract 2017;8:401–6.
[19] Qureshi UA, Sami A, Altaf U, et al. Thiamine responsive acute life threatening metabolic acidosis in exclusively breast-fed infants. Nutrition 2016;32:213–6.
[20] Bhat JI, Rather HA, Ahangar AA, et al. Shoshin beriberi-thiamine responsive pulmonary hypertension in exclusively breastfed infants: a study from northern India. Indian Heart J 2017;69:24–7.
[21] Qureshi UA, Wani NA, Ahmad K, et al. Infantile Wernicke's encephalopathy. Arch Dis Child 2015;100:648.
[22] Sachdev HPS, Shah D, et al. Thiamine (vitamin B1). In: Kliegman RM, St Geme JW III, Blum NJ, editors. Nelson textbook of pediatrics, 21st ed., Canada: Elsevier; 2019.
[23] Lonsodale D. Thiamine deficiency and sudden deaths. Lancet 1990:336–76.

[24] Wani NA, Qureshi UA, Ahmad K, et al. Cranial ultrasound in infantile encephalitic beriberi: a useful first-line imaging tool for screening and diagnosis in suspected cases. AJNR Am J Neuroradiol 2016;37:1535–40.
[25] Bhat JI, Ahmed QI, Ahangar AA, et al. Wernicke's encephalopathy in exclusively breastfed infants. World J Pediatr 2017;13:485–8.
[26] Rao SN, Mani S, Madap K, et al. High prevalence of infantile encephalitic beriberi with overlapping features of Leigh's disease. J Trop Pediatr 2008;54:328–33.
[27] Kornreich L, Bron-Harlev E, Hoffmann C, et al. Thiamine deficiency in infants: MR findings in the brain. AJNR Am J Neuroradiol 2005;26:1668–74.
[28] Wani NA, Qureshi UA, Jehangir M, et al. Infantile encephalitic beriberi: magnetic resonance imaging findings. Pediatr Radiol 2016;46:96–103.
[29] Fattal-Valevski A, Kesler A, Sela BA, et al. Outbreak of life-threatening thiamine deficiency in infants in Israel caused by a defective soy-based formula. Pediatrics 2005;115:e233–8.
[30] Tanphaichit V. Thiamin. In: Shills ME, Olson JA, Shike M, Ross AC, editors. Modern nutrition in health and disease, Philadelphia: Lippincott, Williams and Wilkins; 1999. p. 381–9.
[31] Singleton CK, Martin PR. Molecular mechanism of thiamine utilization. Curr Molec Med 2001;1:107–97.
[32] Sebrell J W. A clinical evaluation of thiamine deficiency. Ann N Y Acad Sci 1962;98:563–7.