

Infantile Thiamine Deficiency: New Insights into an Old Disease

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Context: The wide spectrum of clinical presentation in infantile thiamine deficiency is difficult to recognize, and the diagnosis is frequently missed due to the lack of widespread awareness, and non-availability of costly and technically demanding investigations. **Evidence acquisition:** The topic was searched by two independent researchers using online databases of Google scholar and PubMed. We considered the related studies published in the last 20 years. The terms used for the search were 'thiamine', 'thiamine deficiency', 'beriberi', 'B-vitamins', 'micronutrients', 'malnutrition', 'infant mortality', 'Wernicke's syndrome', 'Wernicke's encephalopathy', and 'lactic acidosis'. **Results:** In the absence of specific diagnostic tests, a low threshold for a therapeutic thiamine challenge is currently the best approach to diagnose infantile thiamine deficiency in severe acute conditions. The practical approach is to consider thiamine injection as a complementary resuscitation tool in infants with severe acute conditions; more so in presence of underlying risk factors, clinically evident malnutrition or where a dextrose-based fluid is used for resuscitation. Further, as persistent subclinical thiamine deficiency during infancy can have long-term neuro-developmental effects, reasonable strategy is to treat pregnant women suspected of having the deficiency, and to supplement thiamine in both mother and the baby during breastfeeding. **Conclusions:** Health care professionals in the country need to be sensitized to adopt a high level of clinical suspicion for thiamine deficiency and a low threshold for the administration of thiamine, particularly when infantile thiamine deficiency is suspected.

Keywords: Beri-beri, Micronutrients, Mortality, Nutrition, Vitamin B.

Thiamine is a water-soluble B vitamin that plays important co-enzymatic and non-co-enzymatic roles within the body [1]. In addition to its role in the metabolism of carbohydrates and amino-acids, thiamine is essential in the synthesis of nucleic acids, myelin, and neurotransmitters (acetylcholine) [1]. Recent evidence suggests that thiamine may have a role in immunity, anti-inflammation and gene regulation [1-2]. Thiamine is an essential vitamin with no endogenous source of synthesis within humans and needs to be continuously supplied in the diet. In addition, the body stores are limited and the turnover rate is high (half-life <10 days) making it potentially susceptible to depletion. In conditions of insufficient intake, thiamine deficiency can develop over a period of 2-3 months [3,4].

The global prevalence of thiamine deficiency is poorly documented due to a dearth of population-level biomarker data [5]. Studies from South-East Asia have reported a prevalence of 27-78% in mothers and 15-58% in children [1,3,5]. The prevalence in children admitted to hospitals ranges from 13-30% in South Asia and around 40% in Africa [3,5,6]. In India, there are limited reports of thiamine deficiency in the pediatric population [7-9].

In infancy, thiamine deficiency has a wide range of clinical presentations, with high fatality in untreated cases,

and survivors usually have long-term sequelae. Although thiamine deficiency is effectively treatable, it continues to affect infants in both developed and underdeveloped countries, and with potentially serious and life-threatening consequences [3,8-10]. This review was undertaken in view of recent reports of infantile thiamine deficiency from this region in Northern India. [13-18]. The review also becomes important as current research suggests role of thiamine deficiency in sepsis/septic shock, and induced-thiamine deficiency in re-feeding syndrome [3]. This review was further prompted by longitudinal evidence suggesting potential adverse long term implications of subclinical infantile thiamine deficiency on neuro-development in later childhood [19-21].

THIAMINE BIOLOGY

Thiamine (vitamin-B1) is a water-soluble vitamin found in several food products including meat, fish, seeds, nuts, green peas, sunflower seeds, beans, and soy products [5,22]. In children, the estimated daily recommended dietary allowance (RDA) is 0.5mg/day for 1-3 years, 0.6 mg/day for 4-8 years, 0.9 mg/day for 9-13 years, and 1-1.2 mg/day for 14-18 years of age [22]. The RDA for adult men is 1.1 mg/day, adult women is 1.2 mg/day; and for women during pregnancy and lactation RDA is 1.4 mg/day [22]. Breast milk has a thiamine content of

around 0.21 mg/L but it may vary depending on the diet and the geographical region [5,22].

Absorption: Thiamine absorption is most efficient in the upper jejunum and to a lesser amount in the duodenum and ileum [23]. Thiamine is absorbed in its free, non-phosphorylated form into the intestinal mucosal cells [23,24]. The small intestine has a dual system of thiamine absorption either through an active carrier-mediated or *via* a passive diffusion process [23-25]. Once inside the mucosal cell, thiamine is phosphorylated to thiamine diphosphate by thiamine pyrophosphokinase, before it is transported to the opposite pole [25].

Distribution: On the basolateral membrane of intestines, thiamine is transported by a thiamine/H⁺ antiport system into the portal circulation [26]. Thiamine targets the cells that utilize glucose as the main energy source; however, thiamine tissue tropism is primarily determined by the degree of expression of key transporters on cell membranes in the major body systems of splanchnic, muscular, nervous, renal systems, and the placenta [27, 28].

Pathophysiology of Deficiency

Thiamine is present in the body as free thiamine, as well as in several phosphorylated forms: thiamine monophosphate (TMP), thiamine diphosphate (TDP), and thiamine triphosphate (TTP). TDP also called thiamine pyrophosphate, is the metabolically active and the most abundant form of thiamine in the body (>80%) [29,30]. Thiamine plays essential coenzyme and non-coenzyme roles in energy transformation, synthesis of pentoses and nicotinamide adenine dinucleotide phosphate (NADPH), and membrane and nerve conduction [29]. In energy transformation, thiamine is a cofactor in multiple enzyme complexes involved in the metabolism of carbohydrates and amino acids, particularly pyruvate dehydrogenase complex (PDH), and α -ketoglutarate dehydrogenase complex (α -KGDH) [31] (**Fig. 1**).

There are fundamental variations in the distribution of thiamine derivatives in human brain, with compartmentalization of thiamine dependent enzymes in areas specifically involved in cerebral glucose and energy utilization [1-3]. Therefore thiamine deficiency causes preferential injury in areas which have high metabolic requirement and high thiamine turnover rate [3]. This explains the specific brain imaging findings with dominant involvement of basal ganglia, which are known to have abundant mitochondrial density and a rich vascular supply [15,17]. Further, studies have reported that transketolase present in myelinated neurons is responsible for maintaining myelin sheaths. The neurological aberrations

observed in thiamine deficiency may, therefore, be due to a lack of energy, a decreased amount of acetylcholine, and/or a reduction in nerve impulse transmission [1,32]. Similarly, muscle cells, particularly cardiac myocytes, with high energy utilization are predominantly involved in thiamine deficiency, giving rise to early manifestations such as the muscle weakness, paresis of gastrointestinal tract, pulmonary hypertension and heart failure [3,13].

RISK FACTORS FOR THIAMINE DEFICIENCY

Thiamine deficiency is rare in healthy individuals in food-secure settings, where access to thiamine-rich foods ensures adequate intakes. Deficiency can result from various mechanisms which include: decreased nutrient intake, increased nutrient losses, impaired nutrient absorption or increased demand [3,33,34] (**Box I**).

Risk factors in infancy: Infants are particularly susceptible to thiamine deficiency in the initial months of life, and exclusively breastfed infants of thiamine-deficient but otherwise asymptomatic mothers are at the highest risk. Studies have shown that thiamine content in breast milk is directly related to the status of thiamine in the nursing mother [34,35]. Additionally, certain customary habits like dietary restrictions in mothers also contribute to the deficiency in some communities. Further, associated co-morbidities are common in infants and increase the risk of thiamine deficiency, like sepsis and shock are frequent during complicated severe acute malnutrition and contribute to the increased mortality [5].

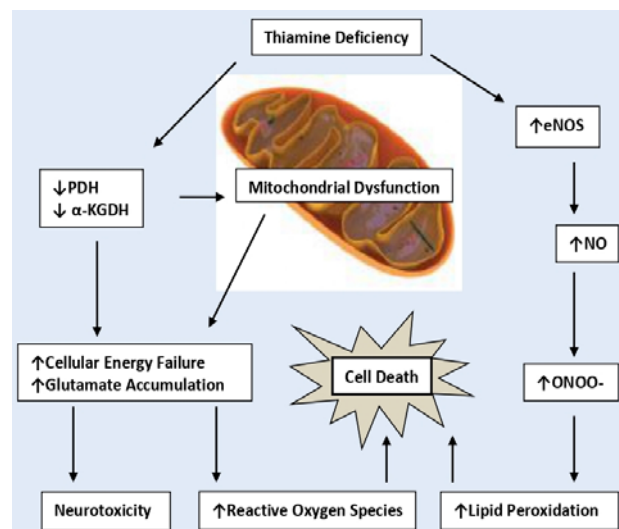


FIG. 1 Thiamin deficiency induced neurotoxicity, lipid peroxidation, and cell death. α -KGDH- α -ketoglutarate dehydrogenase; eNOS-epithelial nitric oxide synthase; NO-nitric oxide; ONOO-peroxynitrate; PDH-pyruvate dehydrogenase.

Box I RISK FACTORS FOR THIAMINE DEFICIENCY DISORDERS*Decreased nutrient intake*

- Low socioeconomic status
- Rural background
- Monotonous diets based on milled white cereals, like polished rice (the rich thiamine envelop removed by polishing and repetitive washing) and wheat flour
- Customary dietary restriction
- Exclusive breast feeding
- Delayed introduction of complementary feeding
- Starvation
- Patients on Total parenteral nutrition
- Anti-thiamine factors in diet like tea leaves, betel nuts, coffee, fermented raw fish, mycotoxins

Increased nutrient losses

- Renal loss – loop diuretics, osmotic diuretic diuresis
- Digestive losses – chronic diarrhea, hyperemesis
- Hemodialysis, continuous renal replacement therapy

Increased demand

- Pregnancy
- Lactation
- Critical illness
- Refeeding syndrome
- High carbohydrate or saturated fat diets
- Heavy alcohol drinking
- Inadequate thiamine-caloric ratio in dextrose-based fluid resuscitation
- Vaccination

Impaired absorption

- Impaired intestinal absorptive capacity during malnutrition
- Tropical enteropathy
- Secondary to surgical resection of large portions of the gastrointestinal tract

In developed countries, infantile thiamine deficiency outbreaks have been periodically described [10,36]. One such outbreak in Israel in the year 2003 was due to thiamine-deficient soya formula, and had a high fatality rate [10]. Infantile thiamine deficiency is sometimes reported in intensive care units in patients receiving total parenteral nutrition without thiamine supplementation or in patients receiving prolonged but inadequate thiamine dose [36]. Recently, thiamine deficiency is increasingly being recognized in infants with delayed introduction of complementary diet in at-risk populations [5].

The recent reports of thiamine deficiency from Kashmir were mainly attributed to the local diet that largely consists of polished, unfortified rice [13-18]. All the cases occurred in infants who were exclusively breastfed, and most mothers followed a customary dietary restriction during the postpartum period.

SPECTRUM OF CLINICAL PRESENTATION

Thiamine deficiency classically known as beriberi has a wide range of clinical presentation in infants. Based on the age three clinical forms have been identified in infants: pernicious or cardiac, aphonic form, and pseudo-meningitic form [4,37] (**Box II**). Whilst, the dominant organ system involvement varies considerably in different Indian studies, there is a consistent pattern in terms of underlying risk factors for thiamine deficiency [7,8,13,14] (**Table I**).

Long-term and Subclinical Consequences

Infants who survive the severe acute thiamine deficiency may demonstrate marked intellectual and motor disabilities, microcephaly, seizures, auditory impairment, and various degrees of heart block [19]. In addition to the acute clinical forms described, more subtle and predominant neurological impairments have also been reported and ascribed to underlying chronic subclinical thiamine deficiency in infancy. These include abnormalities in cognitive and psycho-motor development, aberrations in syntactic and lexical modalities of language acquirement, and seizures [20,21]. Longitudinal studies of the survivors of 2003 Israeli outbreak of thiamine deficiency have reported long-term neurological, developmental, and gross motor impairments in children with persistent subclinical deficiency in the first year of life [10,20,21].

Severe Acute Clinical Scenarios Associated with Thiamine Deficiency

Common differentials for thiamine deficiency in infants include sepsis, encephalitis, meningitis, cardiomyopathy, seizure disorder, cerebral malaria, infantile kwashiorkor, vitamin A intoxication, Leighs disease, metabolic encephalopathy, idiopathic pulmonary arterial hypertension, among others [37].

Functional or true thiamine deficiency has been found to be associated with various severe acute conditions in children and adults. In a Brazilian study, the prevalence of thiamine deficiency was 28% in sick infants admitted to pediatric intensive care units [38], and there was documented biochemical evidence of deficiency in approximately 13.4% of critically ill infants without actual clinical evidence of beriberi [40]. This may be a reason for the poorer prognosis of septic shock in complicated severe

Box II CLINICAL SPECTRUM OF THIAMINE DEFICIENCY DISORDERS*Pernicious or acute cardiac form*

- Peaks at 1- 3 mo of age, starts with non-specific symptoms
- Refusal to feed
- Emesis, constipation
- Tachypnea
- Agitation
- Loud piercing incessant crying progressing to aphonia.
- Acute congestive cardiac failure with cyanosis and edema.
- Rapidly progressive and fulminant form with no edema (Shoshin beriberi) in certain infants.

Aphonic form

- Less severe form: predominates at 4–7 mo
- Aphonia due to paresis (or paralysis) of the vocal cords
- Untreated cases advance into cardiac and respiratory failure, death within days-weeks

Pseudomeningitic form: 6-12 mo old.

- Muscular fasciculation
- Nystagmus, Ophthalmoplegia
- Tense fontanel
- Seizures, and coma
- Clinical signs of meningitis, but cerebrospinal fluid findings excludes infection.

Encephalopathic form

- Usually older children and adults, sometimes in infants
- Ophthalmoplegia, nystagmus
- Ataxia.
- Reduced consciousness
- Coma and death.
- A truncated Wernicke-like syndrome with-out ataxia may also develop in some children

Neuropathic form

- Latter half of infancy, older children and adults
- Muscle pains
- Diminished or abolished deep tendon reflexes
- Ataxia
- Muscle wasting
- Cranial nerve involvement

acute malnutrition, with potential thiamine deficiency precipitated by sepsis [39]. Moreover, the development of re-feeding syndrome during the management of severe acute malnutrition (SAM) may contribute to the higher

mortality, particularly when there is rapid introduction of feeds in children with pre-existing depleted body stores of thiamine. During nutritional resuscitation, rapid commencement of feeds triggers insulin production leading to enhanced protein synthesis and heightened cellular glucose metabolism, and consequent higher metabolic thiamine utilization and demand [41-43]. This induced deficiency along with the signs of re-feeding syndrome are often over-looked or misinterpreted as sepsis, pneumonia, encephalitis, cardiac failure or sudden death [42].

In addition, recent studies have attributed underlying thiamine deficiency for the increased mortality in patients with lactic acidosis in acute severe conditions and shock [39,44]. Moreover, in intensive care units, risk of deficiency increases during hospital stay, as sick children are often fasting for prolonged periods, and parenteral nutrition is most often lacking, more so in resource-poor settings.

Broadly, in the acute care setting, underlying thiamine deficiency should be suspected in children with persistent lactic metabolic acidosis or elevated plasma anion-gap, cardiogenic shock unresponsive to appropriate therapy, and in any condition that results in increased thiamine demand (hypermetabolic states) such as sepsis, shock, poly-trauma, large burns, diabetic ketoacidosis, congenital heart disease, and severe malaria [3-5,14,32,38]. Further, thiamine deficiency should be kept as a possibility whenever there are unexplained severe neurological signs in infants without clinical evidence of true thiamine deficiency [3].

EVALUATION

Thiamine status can be determined by analysis of plasma, serum or whole blood; however, it represents only a small part of the whole body thiamine pool [11]. TDP levels provide a better measure of body thiamine status but do not assess thiamine metabolic function. Erythrocyte transketolase activity (ETKA) is more accurate in assessing the functional thiamine status of the body (**Table II**). Thiamine is excreted in urine, mainly as free thiamine and TMP, and levels <40 µg/day or <27 µg/g creatinine can be taken as suggestive of thiamine deficiency [3,4,11].

Concentration of pyruvate or lactate in the blood can also be used to assess the thiamine status but these measurements are limited by a lack of specificity [11,14]. Specific lesions in certain areas of the brain on MR imaging can be helpful in early identification of neurologic involvement in thiamine deficiency. MRI of Wernicke's syndrome in infants displays lesions in the frontal lobe and

TABLE I CLINICAL CHARACTERISTICS OF THIAMINE DEFICIENCY REPORTED IN DIFFERENT INDIAN STUDIES

	<i>Bhat, et al.</i> 2017 [11]	<i>Qureshi, et al.</i> 2016 [12]	<i>Rao, et al.</i> 2010 [36]	<i>Rao, et al.</i> 2008 [35]
Study sample size (<i>n</i>)	29	23	55	166
Age at presentation (mo)	2.6	1.7	3.9	7
Exclusive breast-fed, %	100	100	100	100
Dominant clinical syndrome	PAH	Life-threatening metabolic acidosis	PAH with right heart failure	Infantile encephalitic
<i>Systemic features, %</i>				
Fever	31	21	52.7	72.2
Reduced feeding	–	34	–	–
Failure to thrive	–	4	–	–
Reflux	–	56	–	44
<i>Cardiovascular, %</i>				
Tachycardia	86.2	100	100	–
Poor perfusion	75.8	52	–	–
Edema	65.5	–	10.9	–
TR murmur	93	–	–	–
<i>Respiratory, %</i>				
Tachypnea	68.9	–	100	–
Gasping breathing	17.2	–	–	93.5
Apnea	–	–	–	6.5
Hoarseness of voice and/or aphonia	–	4	–	18.2
<i>Central nervous system, %</i>				
Irritability	82.7	82	–	–
Lethargy	–	8	–	63.3
Vacant stare	13.7	13	–	–
Ptosis	–	13	7.3	76
Seizures	–	26	–	55.4
Moaning	–	73	–	–
<i>Gastrointestinal, %</i>				
Diarrhea	–	13	–	–
Hepatomegaly	100	–	–	80

PAH: pulmonary arterial hypertension; TR: tricuspid regurgitation.

basal ganglia, chiefly the striatum and putamen. In addition, both adults and children with thiamine deficiency exhibit the same symmetrical high-intensity signal on T2 weighted MRI in mammillary bodies, peri-aqueductal and thalamic areas [7,15,17]. MR findings reported in Western literature also demonstrated lesions in the basal ganglia and frontal lobes [45]. However, Indian studies reported dominant basal ganglia (putamina) lesions with infrequent involvement of thalamic, cortical, brainstem and mammillary bodies [15,35]. Recently, cranial ultrasonography was observed to have utility as a first-line screening and diagnostic tool in infantile encephalitic beri-beri [15]. Basal ganglia hyperechogenicity on neurosonogram was

reported to have a sensitivity and specificity of 71% and 92%, respectively, with maximum sensitivity in Wernicke-like syndrome at 90% and least in the acidotic form at 43% [15].

TREATMENT

Though thiamine assessment prior to repletion may be used to confirm the suspected deficiency, serious and potentially irreversible neurologic damage can occur in untreated cases. In such contexts the ideal approach is a high index of clinical suspicion and early therapeutic thiamine challenge, which is the treatment of suspected cases without laboratory confirmation and monitoring for

TABLE II BIOMARKERS USED TO MEASURE THIAMINE STATUS

<i>Biomarker</i>	<i>Specimen</i>	<i>Normal value</i>	<i>Advantages</i>	<i>Disadvantages</i>
<i>Direct assessment</i>				
Thiamine	Plasma	75 to 195 nmol/L	Indicates recent intake	Represents a small part (<10%) of the whole body thiamine pool Low specificity and sensitivity
ThMP	Plasma		Indicates recent intake	Not an indicator of thiamine status
ThDP	Whole blood Erythrocytes	70 to 180 nmol/L	Dominant form (~80%) of thiamine in erythrocytes. Better measure than total thiamine.	Does not assess thiamine metabolic function. Unstable if specimen is not handled properly.
<i>Indirect/functional assessment</i>				
ETKA	Washed erythrocytes. Increase in ETKA with the addition of thiamine to the incubation medium	Increase of >25% indicates high risk of deficiency, Increase between 16% and 25% indicates moderate risk	Functional assay of biological activity	Expensive Time consuming Not readily available

ThMP: thiamine monophosphate; ThDP: thiamine diphosphate; ETKA: erythrocyte transketolase activity.

the resolution of signs and symptoms [36]. Considering the safety profile and a wide dosage range (50 to 1500 mg) in such cases, thiamine can be administered as a slow intravenous injection. In severe acute conditions due to thiamine deficiency, rapid clinical improvement occurs (within hours or days) following thiamine administration, with neurological involvement requiring higher doses and often taking a longer time to recover (few days) [4,11]. Treatment or prevention of induced-deficiency in refeeding syndrome needs proper adjustments in volume and calorie density of feeds, gradual correction of electrolyte disturbances and adequate supplementation of thiamine in therapeutic diets. Current recommendation is to administer 2 mg/kg of thiamine daily during the first week of SAM management [46,47]. As ready-to-use therapeutic foods (RUTF) [either F-75 (75 kcal/100 mL) or F-100 (100 kcal/100 mL)] contain an average of 0.5 mg of thiamine per sachet, proper attention to additional supplementation is needed during the initiation phase of SAM management [48]. Moreover, infants under 6 months of age with SAM receive either breast milk or diluted RUTF, putting them at higher risk of thiamine deficiency, particularly when the mothers are not properly supplemented. Therefore, Infants under 6 months need to be supplemented with 2 mg/kg of thiamine daily in order to mitigate the risk of inducing thiamine deficiency during SAM management [3,5,46,47].

CURRENT INDIAN SCENARIO

Most of the literature on micronutrients relating to the Indian scenario focuses on deficiencies of iron, vitamin A and iodine, and less attention has been given to vitamin B deficiencies, including thiamine. The actual prevalence and potential contribution of thiamine deficiency disorders to the infant mortality in India are not known and is mostly considered as an association with other deficiencies in severe acute malnutrition [9].

Though most of the studies on infantile thiamine deficiency are from South Asian countries, it has been reported from different parts of India as well. One study from India reported a high prevalence of a form of infantile encephalitis with overlapping features of Leigh's disease, with a dramatic response to thiamine supplementation, suggesting a diagnosis of thiamine deficiency. The diagnosis was later confirmed in most of the patients by ETKA analysis [7]. This study highlighted the importance of thiamine deficiency in Indian context after it was reported to have been eliminated from India in 2004 [49]. A review on micronutrient deficiencies in Indian children concluded that sub-clinical B vitamin deficiencies are quite rampant in India, and that they are likely to have long-term functional effects that track into adulthood [48]. More recently, the reports of high prevalence of thiamine deficiency in exclusively breastfed infants from Kashmir valley strengthened the argument that thiamine deficiency

in India is far from controlled and may warrant a relook [13-18]. Furthermore, recent research has shown that even subclinical thiamine deficiency in infancy can have a long-term negative impact on cognitive behaviour and learning. Although in India, reported clinical cases are only clustered around certain specific regions [7,8], it may be reasonable to surmise a sub-clinical thiamine deficiency elsewhere in the country. This is particularly important as the other micronutrient deficiencies in Indian children are quite rampant [9].

Further, the overall clinical picture of thiamine deficiency is not easy to recognize, and diagnosis is quite often missed due to lack of awareness and non-availability of a confirmatory test, which is expensive and technically demanding. Not surprising, the chances of misdiagnosis is even greater in resource-poor setting [3,36,38]. In the absence of specific diagnostic tests, a low threshold for a therapeutic thiamine challenge is the only way to diagnose thiamine deficiency. The practical approach is to consider thiamine injection as a complementary resuscitation tool in infants with severe acute conditions; more so in presence of underlying risk factors, clinically evident malnutrition or where a dextrose-based fluid is used for resuscitation [3,4,8].

Considering the possibility of long-term neurodevelopmental consequences of persistent subclinical thiamine deficiency in the infantile period, pregnant women suspected of having thiamine deficiency should be adequately treated and the supplementation should be continued in both mother and baby during breastfeeding. Additionally, there is a need to sensitize health care workers in the country to develop a high level of clinical suspicion for thiamine deficiency and a low threshold for the administration of thiamine, particularly when infantile thiamine deficiency is suspected. Moreover, obstetricians need to be sensitized regarding supplementation of thiamine in diet of at-risk pregnant and lactating mothers. Besides, nutrition rehabilitation centers and pediatricians need to be cautioned about the possibility of refeeding syndrome and induced- thiamine deficiency in children with SAM.

Further, at the community level improvised strategies like programmatic approaches to fortification, supplementation, dietary modification (like parboiling of rice) and education, and training of healthcare workers, are needed to improve overall thiamine status of our population. Studies providing objective and demonstrable evidence of the possible contribution of thiamine deficiency to infant mortality rates in India are needed. More importantly, studies in high-risk communities will be needed to galvanize the states to develop measures for

early diagnosis, treatment and long-term prevention of thiamine deficiency in infancy. Lastly, additional research is needed to understand the long-term developmental effects of subclinical thiamine deficiency and to identify the factors that may trigger overt clinical disease in such deficient children.

CONCLUSIONS

Infantile thiamine deficiency continues to be an important cause of mortality and long-term morbidity in infants in developing countries. Due to a wide range of clinical presentation deficiency is often overlooked or mistaken for other acute problems in the infantile period. Apart from causing infant mortality, thiamine deficiency may have an unappreciated long-term impact on neurological development in children with persistent subclinical deficiency during infancy. A high index of suspicion and a low threshold for the administration of thiamine is needed to prevent acute and long-term complications. Additionally, there is a need to sensitize health care workers in the country about the clinical spectrum, diagnosis and early treatment of thiamine deficiency in infants.

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