High Prevalence of Infantile Encephalitic Beriberi with Overlapping Features of Leigh's Disease

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Summary

Infantile encephalitic beriberi (IEBB) is a rare form of thiamine deficiency and is poorly described. A proportion of Leigh's disease (LD) patients have similar clinical picture and response to thiamine as beriberi, leading to confusion in diagnosis and management. Data on IEBB and LD is scarce and status of thiamine deficiency in India is controversial. We report several infants with life-threatening respiratory and central nervous system symptoms that overlap between IEBB and LD. Majority had low erythrocyte transketolase levels and responded dramatically to thiamine supplementation suggesting a diagnosis of IEBB. However, presence of characteristic lesions on brain imaging and residual damage in several patients on follow-up does not rule out LD completely. Our study highlights the importance of thiamine deficiency in India, especially in the breast-feds and its overlapping features with LD. Awareness of this common mode of presentation may save patients' lives by early diagnosis and timely thiamine supplementation.

Key words: Thiamine deficiency, nutrition—infant, infantile encephalitic beriberi, Leigh's disease, public health.

Introduction

Thiamine is an essential micronutrient that plays a vital role in the development of brain especially in infants [1]. Its deficiency is known to lead to various manifestations due to damage to the peripheral nervous system or cardiovascular system, commonly known as dry and wet beriberi, respectively [2]. However, another form of beriberi, known as Infantile encephalitic beriberi (IEBB) presenting with acute neurological symptoms is relatively rare and has not been well described in the literature [2]. The clinical picture as well as the imaging findings of IEBB are known to overlap with Leigh's disease (LD), which is a progressive neurometabolic disorder usually presenting in infancy or childhood [2–4]. Similar to a dramatic response to thiamine supplementation in beriberi, a type of LD due to pyruvate dehydrogenase deficiency responds equally well to treatment with thiamine [5]. Due to these overlapping features, the two conditions are commonly misdiagnosed unless one has good clinical acumen and shows a high index of suspicion.

Beriberi, although uncommon, can be found among alcoholics and is known to appear, in breast-fed infants when the mother has an inadequate intake of thiamine or if the infant is fed unusual formulas without thiamine supplements [6]. Severe thiamine deficiency has been a problem of developing countries and developed countries are said to have overcome it through enrichment of most foods [6]. It has been reported in 2004 and again recently that India has eliminated beriberi through programs such as under milling of rice [7, 8]. Similarly, there are few isolated case reports of LD and the disease has hardly been explored in India [9–11].

We recently cared for several infants who presented with life threatening respiratory and neurological symptoms that required hospitalization and management in the emergency ward of our hospital. All the infants had a clinical picture that overlapped

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between LD and IEBB and responded remarkably to large dose of thiamine. These observations prompted speculation about thiamine deficiency and its clinical presentation either as IEBB or LD. LD, which is a rare disease, usually has a subacute or chronic presentation; however, it may also present with acute life-threatening features. There are very few reports of such cases from India [5]. Since, IEBB due to thiamine deficiency and LD are known to have common characteristics [2, 4, 12] and since an exact diagnosis has therapeutic and prognostic implications, we investigated these patients further to understand the exact nature of pathology in them. Detailed biochemical and neuro-imageological investigations and follow-up of the clinical course of these cases may highlight the possibility of a high prevalence of sub-clinical thiamine deficiency due to dietary or other factors and its clinical consequences. We also want to highlight this condition since a proper diagnosis can aid in early management with thiamine supplementation.

Materials and Methods

During the year 2003, several infants were referred with a diagnosis of meningitis to the Niloufer Hospital for Women and Children, a tertiary referral center at Hyderabad, in southern India. These infants presented with impaired consciousness, seizures and irregular respiration. All such patients were further investigated as per a standard questionnaire, which included a detailed clinical history and thorough examination, biochemical investigations such as serum amino acids, blood and cerebrospinal fluid (CSF) lactate levels, radiological examination with computed tomography (CT) and/or magnetic resonance imaging/spectroscopy and neurosonogram (MRI/MRS & NSG), the morbidity and mortality pattern and response to thiamine supplementation. Initial diagnosis was mainly based on the clinical picture. Estimate of thiamine levels was obtained through measurement of erythrocyte transketolase (TK) activity in several patients (before and after thiamine treatment) and in some of the mothers, who gave informed consent [13]. TK requires thiamine pyrophosphate as a cofactor to catalyze two reactions involved in glucose oxidative pathway, hence, patients showing reduced TK activity reflect their thiamine deficient status. This procedure was based on disappearance of pentose as measured by orcinol reaction [13]. Management of the patients including thiamine supplementation (200–300 mg per day) started immediately after collecting appropriate blood samples. A detailed proposal with the design of the study and format for the informed consent was submitted to the Institutional ethics committee (IEC) of Centre for Cellular and Molecular Biology, Hyderabad and Government Institute of Child Health, Niloufer Hospital for Women and Children, Hyderabad, India. Written informed consent was obtained from the parents in accordance with the IEC approved protocols. The patients were advised to continue with 75 mg per day thiamine for 3 months after discharge. Several patients were followed–up at different time intervals with specific stress on clinical evaluation and neuro-imaging investigations was repeated on few of them.

Results

A total of 166 children with the aforementioned clinical picture were recruited in the study. The majority were infants with no bias in sex distribution and mean age of onset at 7 months. Detailed history revealed that all the infants were exclusively breast-fed and their mothers came from a rural background and low socio-economic status. Their staple diet consisted of non-parboiled polished rice with rice ganji (soup) strained after cooking and meagre amount of vegetables. Additionally, as part of cultural practice, the womenfolk would eat the food that remained after serving the whole family.

Most of the patients presented with severe respiratory irregularities. Common clinical manifestations included altered sensorium, external ophthalmoplegia, seizures, hypotonia, characteristic irregular sighing or sobbing respiration along with a history of fever and vomiting (Table 1). Associated features included aphonia, choreo-athetoid movements, arreflexia and loss of milestones with head lag. Serum and CSF lactate levels were high while serum amino acid profile and routine CSF analyses were normal. TK levels were less than 7.5 IU (normal range, 12–18 IU) in the infants, while a few mothers who agreed to participate showed borderline levels (8.5–11 IU) [13]. TK levels returned to normal range in the patients on repeat analysis within few days. Brain imaging showed characteristic symmetric hypodense lesions in the basal ganglia on CT and/or hyper-intense lesions on T2-weighted MRI in the majority with similar lesions in thalamic and brain stem regions in few cases (Fig. 1) [4, 14, 15]. MRS could be performed in only 17 patients, 10 showed a lactate peak [16]. Certain investigations could not be performed in four cases as they were critical on admission and expired before thiamine supplementation could be instituted.

Thiamine supplementation produced a remarkable response and reduced the morbidity and mortality significantly. Within 24 h the first signs of improvement were noted in the level of consciousness, respiratory abnormalities and ptosis whereas head control, tone, involuntary movements and milestones recovered partially over next few weeks. Since most of the patients were illiterate and lived in rural areas, we could follow only 26 patients. All 15 patients who were re-examined within 3–6 months of initial illness, were clinically normal except two who still had

TABLE 1
Characteristics of the study population

n	166
Age in months (median, 95% CI)	7.0 (6.7–7.7)
Sex (M/F)	78/88
Clinical features	
Fever	120 (72.2)
Vomiting	73 (44.0)
Central nervous system	
Seizures	92 (55.4)
Altered sensorium	105 (63.3)
Loss of milestones	143 (86.1)
External ophthalmoplegia/Ptosis	126 (76.0)
Nystagmus	8 (4.8)
Developmental delay	11 (6.6)
Involuntary movements	64 (38.5)
Tone	
Decreased	126 (76.0)
Increased	8 (4.8)
Normal	32 (19.2)
Respiratory disturbances	123 (74.1)
Irregular breathing with sighing or sobbing	115 (93.5)
Apnoea	8 (6.5)
Biochemical parameters	
Serum Lactate	144 (86.7)
Increased	104 (72.2)
Normal	40 (27.8)
Imageology	
CT scan	141 (85.0)
Abnormal	116 (82.3)
Normal	25 (17.7)
MRI	26 (15.6)
Abnormal	25 (96.2)
Normal	1 (3.8)
MRS	17 (10.2)
Lactate peak	10 (58.8)
Normal	4 (23.5)
Inconclusive	3 (17.6)
NSG	119 (71.6)
Abnormal	77 (64.8)
Normal	42 (35.2)

n, number of patients; 95% CI, 95% confidence interval; Figures in parentheses indicate percentage; CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NSG, neuro-sonogram.

hypotonia, delayed milestones and persistence of brain lesions on imaging. Complete resolution of earlier central nervous system lesions was found in six out of eight cases with abnormal CT findings at initial diagnosis, whereas seven remaining cases with an initial normal CT did not show any new lesions. Nine of the eleven patients on long-term follow-up were clinically and on imaging normal while two still had persistence of earlier lesions and commensurate clinical abnormalities. No fresh lesions in other parts of the brain were noted in any of these patients.

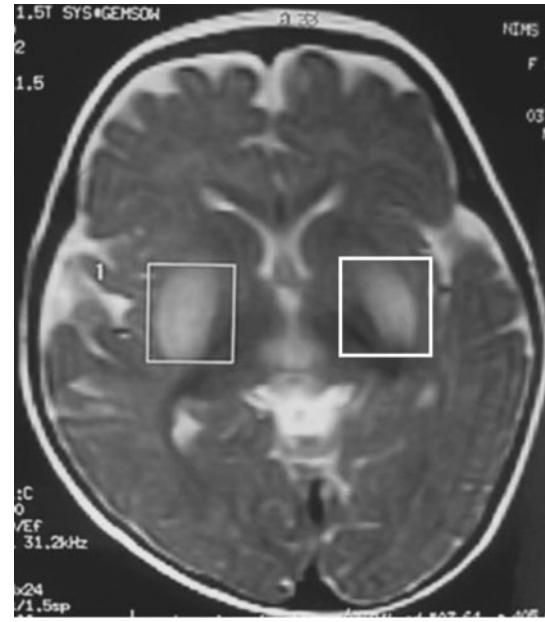

FIG. 1. Magnetic resonance imaging (MRI) picture of a patient showing characteristic bilaterally symmetrical hyper intense lesions in the basal ganglia. The rectangles indicate the lesions on either side.

Discussion

The present study investigated the clinical picture, biochemical parameters, radiological features and the clinical course in a large number of infants presenting with acute neurological manifestations and overlapping features between LD and infantile encephalitic beriberi. Both conditions are commonly misdiagnosed and an accurate diagnosis has important implications in their management [12].

The initial diagnosis is usually based on the characteristic clinical presentation with supporting evidence from biochemical analysis and imaging but in most cases, these are not conclusive [2, 4, 17]. In our study too, most of the patients presented with clinical features such as altered sensorium, acute loss of milestones, ptosis and irregular respiration, with a raised serum and CSF lactate which are common to both IEBB and LD [2–4]. Detailed neuro-imaging also showed lesions that overlap between the two clinical entities. On follow-up, the majority of the patients had complete resolution of the brain lesions, corroborated by clinical improvement; however, few had persistent neurological and imaging abnormalities. The variability of outcome in these patients may be explained by the initial extent of damage and/or relative delay in initiation of treatment with thiamine. Although, a progressive clinical deterioration with imaging evidence is more suggestive of LD

but an alternative cannot be completely ruled out in our patients [17]. Since majority of infants had low TK levels and responded dramatically to thiamine supplementation, IEBB appears to be more probable diagnosis but thiamine responsive LD due to pyruvate dehydrogenase deficiency is an established entity and an important differential diagnosis [5].

LD is thought to be a rare inherited metabolic disorder and is commonly misdiagnosed due to its varied clinical presentation [18, 19]. This is also exemplified by the few case reports in the Indian population [9–11]. Similarly, confusion also prevails regarding thiamine deficiency and its clinical consequences. Dry and wet are the only forms of beriberi that are described in the text books, whereas the acute neurological form better known as IEBB or infantile Wernicke's encephalopathy is hardly emphasized [2, 20]. To make the matter more confusing, though thiamine deficiency is common in many South Asian countries, it has been reported to have been eliminated from India in notifications to the UN Assembly and to the President of India in 2004 [21]. A recent bulletin of The Nutritional Foundation of India reiterated the same and reported that vitamin B1 deficiency has been eliminated by the sensible approach of under milling rice [8]. The aforementioned facts may contribute to frequent misdiagnosis and increased mortality in these cases. Our observation that the majority of patients presented with the above clinical picture following an intercurrent infection suggests that the clinical presentation could be due to increased demand for thiamine during the illness [2]. Thus, there may be a sub-clinical thiamine deficiency in the population, particularly because they belonged to low socio-economic status and their diet consisted of non-parboiled polished rice. Most of the infants in our study were exclusively breast-fed. Many of them came from the same community and ethnic background; their cultural taboos and eating habits might have pre-disposed to thiamine deficiency.

Thus, in contrast to the existing belief, our study suggests that thiamine deficiency does exist in the Indian population and is not very rare. This confusion may have stemmed from the fact that dry and wet beriberi are the only common forms of thiamine deficiency that is published in the literature and an encephalitic form is not well described [2, 19]. Incidentally, some patients on a long-term follow-up in our study did show some evidence of residual neurological damage, raising the possibility of LD, which is thiamine responsive. Further follow-ups at later time may be helpful in resolving these doubts. Although, these patients clustered around a specific region in southern India, it may not be unreasonable to surmise a sub-clinical thiamine deficiency elsewhere in the country. Our study thus, raises an important question regarding the status of thiamine deficiency and its clinical consequences in the Indian population. The fact that we have identified large number of patients with probable diagnostic features of IEBB/LD, underscores the need to undertake large community-based studies and settle the controversy about status of thiamine.

Conclusions

Our study detected large number of pediatric cases over a period of 3 years with overlapping features of Leigh disease and of thiamine deficiency and indicates that thiamine deficiency in India is far from controlled. Clinicians should be aware of the possibility of infantile thiamine deficiency and its typical life-threatening presentation in Indian population since early recognition and timely therapy with thiamine may prevent severe irreparable brain damage as well as death. It is also important that public health officials take note of the benefit of thiamine supplementation since sub-clinical thiamine deficiency remains a distinct possibility in India and other developing countries.

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