Wernicke's encephalopathy in exclusive breastfed infants

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Background: **Kashmir has a population that largely consumes polished rice which is deficient in thiamine. Furthermore, lactating women in this region are prone to severe thiamine deficiency because of their traditional food avoidance practices. Infantile beriberi is common in exclusively breastfed infants of thiamine deficient mothers in Kashmir.**

Methods: **This was a one year prospective hospital-based study. We included 50 exclusively breastfed infants in our study. All patients were evaluated as per unit protocol including complete septic workup and metabolic workup. Most of our patients belonged to low and middle income group families, and mothers were on customary dietary restriction. Demographic and anthropometric data were collected from all the study participants. In addition, data regarding the treatments received by the study population and overall mortality were collected.**

Results: **The mean age, male:female ratio, and mean weight of the study population were 3.15±0.97 months, 1.5:1, and 5.1±1.1 kg, respectively. Traditional food avoidance practices were followed by 80% of the mothers. Irritability was observed in 40 (80%) patients. Blepharoptosis was observed in 30 (60%). Septic workup including cerebro spinal fluid analysis was normal in all patients. Predominant magnetic resonance imaging finding was bilateral basal ganglia hyperintensity. Whole blood thiamine diphosphate levels showed a drastic decrease (10-49 nmol/L). Ten percent of the study infants died.**

Conclusion: **In exclusively breastfed infants, we observed acute infantile encephalopathy with epidemiological, clinical, biochemical, and radiological features suggestive of infantile Wernicke's encephalopathy and a favourable therapeutic response to thiamine supplementation during the acute stage.**

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Key words: **basal ganglia hyperintensity; polished rice; Wernicke's encephalopathy**

Original article

Introduction

Acute infantile encephalopathy encompasses a wide spectrum of disorders; common etiologies include acute viral encephalitis caused by a wide range of common viral infections, bacterial meningitis, rickettsial infections, systemic disorders such as hypoglycemia, hyperglycemia, and hyponatremia, inborn errors of metabolism such as urea cycle defects and fatty acid oxidation disorders,[1] and deficiency disorders such as infantile Wernicke's encephalopathy, particularly in places where polished rice is the staple diet[2] or an infant is on a thiamine-deficient formula.[3] Kashmir is located in Northern India where people exclusively eat polished rice, which contains a negligible amount of thiamine. Furthermore, lactating women in this region are prone to severe thiamine deficiency because of their traditional food avoidance practices and taboos in the postpartum period, during which they consume only meat or chicken soups. Moreover, thiamine requirement increases markedly during periods of stress such as pregnancy, childbirth, and lactation, further depleting the thiamine levels in already deficient individuals. Infantile Wernicke's encephalopathy is a rare condition nowadays; however, epidemics of this fatal disease have been reported among exclusively breastfed infants of thiamine-deficient mothers.[4] Thiamine deficiency has been reported in inhabitants of refugee camps predominantly consuming polished rice.[5,6] For some time, multiple cases of acute infantile beriberi have been reported in this region.[7,8] All major pediatric centers in Kashmir have observed a high prevalence of idiopathic infantile encephalopathy in exclusively breastfed infants with a normal septic and metabolic workup, except for nonspecific lactic acidemia,

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a feature peculiar to high prevalence of thiamine deficiency.

To determine the clinical and radiological profiles of infantile Wernicke's encephalopathy and resolve its symptoms by administering intravenous (IV) thiamine to exclusively breastfed infants from a thiamine-deficient area in Northern India.

Methods

This prospective hospital-based study was conducted from November 2014 to October 2015 in the Department of Pediatrics, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, a tertiary care hospital in northern India. Our study included exclusively breastfed infants aged 1-6 months with acute onset encephalopathy associated with opthalmoplegia and nystagmus. Patients with fever, cerebrospinal fluid (CSF) pleocytosis, positive blood cultures, elevated acute phase reactants, septic focus, and dyselectrolytemia were excluded from the study. All patients were evaluated as per unit protocol including a complete septic workup (complete blood count, acute phase reactants, blood culture, CSF, urine microscopy, and culture sensitivity) and measurement of arterial blood gases, serum electrolytes, serum lactate, blood sugar, serum calcium, serum magnesium, and serum ammonia. In addition, tandem mass spectrometry (TMS), urine gas chromatography-mass spectrometry (GC-MS), brain magnetic resonance imaging (MRI), and cranial ultrasonography were performed. Furthermore, the whole blood thiamine diphosphate (TDP) level was evaluated by high-performance liquid chromatography (HPLC).

Patients from all the districts of Kashmir were included, and most of them belonged to low and middle income group families. Data collected included the name, age, sex, consanguinity, feeding history, and mother's dietary history, history of sib deaths or neurological diseases, developmental history, and birth details. In addition, data regarding the treatments received by the study population and overall mortality were collected; and written informed consent was obtained from all study participants.

Statistical analysis

Data were maintained in Microsoft Excel 2007. Continuous variables with a normal distribution were expressed as mean±standard deviation. Nonparametric continuous variables were expressed as median [interquartile range (IQR)]. Data were tested for normality using the Shapiro-Wilk test, and the results were verified by examining quantile-quantile plots. Data were statistically analyzed using SPSS version 20.

Results

We admitted 79 patients with acute encephalopathy during the one-year study period. Of them, 50 were aged 1-6 months and satisfied the inclusion criteria. All patients were afebrile and exclusively breastfed. The mean age, male:female ratio, and mean weight of the study population were 3.15±0.97 months, 1.5:1, and 5.1±1.1 kg, respectively. Consanguinity was present in 20% of the study population. Furthermore, 90% of the patients belonged to the lower socioeconomic class and 32% were lower segment caesarean section born. Traditional food avoidance practices were followed by 80% of the mothers; thoroughly washed polished rice and meat/chicken soups were a major part of their diet. Table 1 presents the clinical characteristics of the study population. Irritability was observed in 40 (80%) patients with a mean duration of 24 hours. Blepharoptosis, right heart failure, and associated aphonia was observed in 30 (60%), 10 (20%), and 4 (8%) of the patients, respectively. Furthermore, 10 (20%) patients had seizures at presentation and 30 (60%) patients had a history of gastroesophageal reflux. Five (10%) infants died, and most of them presented after 24 hours of appearance of the symptoms. Laboratory parameters of the study population are presented in Table 2. Mean total leukocyte count was 12.96±2.80×$10^3/\mu$L, with a lymphocyte predominance in most patients (5.40±1.00×$10^3/\mu$L). CSF pleocytosis was absent in all patients. All patients had normal CSF protein and glucose levels [median (IQR) of CSF protein and glucose were 23.0 (14.5) mg/dL and 54.0 (27.0) mg/dL,

Table 1. Clinical characteristics of the study population

Parameters	*n* (%)
Gastroesophageal reflux	30 (60)
Seizures	10 (20)
Blephroptosis	30 (60)
Irritability	40 (80)
Right heart failure	10 (20)
Aphonia	4 (8)
Vacant stare	6 (12)

Table 2. Baseline laboratory parameters of the study population

Laboratory parameters	Values
Total leucocyte count (×$10^3/\mu$L), mean±SD	12.96±2.80
Neutrophills (×$10^3/\mu$L), mean±SD	3.80±1.20
Lymphocyte count (×$10^3/\mu$L), mean±SD	5.40±1.00
CSF proteins (mg/dL), median (IQR)	23.0 (14.5)
CSF sugar (mg/dL), median (IQR)	54.0 (27.0)
Serum ammonia (μmol/L), mean±SD	54.84±18.43
Serum lactate (mg/dL), median (IQR)	40.5 (30.0)
Arterial pH, mean±SD	7.23±0.12
Bicarbonate (mEq/L), mean±SD	15.70±5.00
Hypacalcemia, *n* (%)	1 (2)

SD: standard deviation; CSF: cerebrospinal fluid; IQR: interquartile range.

respectively]. The majority of the patients presented with metabolic acidosis with a mean arterial pH of 7.23±0.12 and bicarbonate of 15.70±5.00 mEq/L. Median (IQR) of arterial lactate was 40.5 (30.0) mg/dL. Serum ammonia was measured in 20 patients, and all of them had a normal level (54.84±18.43 μmol/L). Transient hypocalcemia was present in one patient on admission (serum calcium: 7 mg/dL), who responded to IV infusion of calcium gluconate (2 mL/kg). Blood cultures in all the 50 patients remained sterile after 5 days of incubation. MRI showed bilateral basal ganglia in 40 patients, and magnetic resonance spectroscopy (MRS) showed thalamic hyperintensity with double lactate peaks in 24 patients (Fig.). In addition, mammillary bodies were observed in 6 patients, and 10 patients had a normal MRI. TMS and urine GC-MS analyses showed nonspecific lactic acidemia in 62% of the patients. Whole blood TDP levels measured in only 5 patients showed a drastic decrease (10-49 nmol/L).

All patients received supportive care as per the unit protocol. A therapeutic response to thiamine supplementation is crucial for diagnosing acute infantile beriberi;[4] therefore, we empirically administered 100 mg/day of IV thiamine in normal saline for 30 minutes and 10 mg/day of thiamine orally after discharge. No adverse effects of thiamine administration were observed. Most of our patients showed a rapid response to thiamine infusion with rapid improvement in symptoms [median (IQR) duration of encephalopathy: 7 (8) hours]. The symptoms of patients with blepharoptosis and irritability improved rapidly, whereas those of patients with associated aphonia improved the least. Eight patients were discharged with some neurodeficit in the form of aphonia, multiple cranial neuropathies or motor deficits. Median (IQR) duration of initiation of oral feeding was 8 (8.25) hours. Five (10%) patients died in our series who presented to us after 24 hours of development of symptoms and were admitted with severe metabolic acidosis and circulatory failure. Neurological abnormality at discharge was seen in 16% of our patients (Table 3).

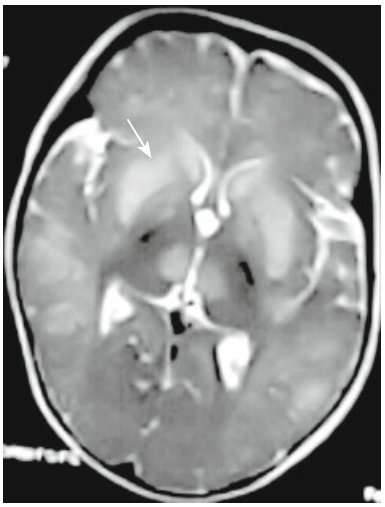

Fig. T2 weighted magnetic resonance imaging of brain showed bilateral basal ganglia hyperintensity (white arrows).

Table 3. Final outcome of the studied population

Parameters	Values
Mortality, *n* (%)	5 (10)
Duration of encephalopathy (h), median (IQR)	7 (8)
Duration of hospital stay (d), median (IQR)	6 (6.25)
Neurological abnormality at discharge, *n* (%)	8 (16)

IQR: interquartile range.

Discussion

Infantile beriberi may be associated with various syndromes, including encephalopathy, right heart failure, hypoglycemia, and severe lactic acidosis.[7] With the advent of mechanical rice milling in the late nineteenth century, beriberi became a dominant public health problem in some countries. In a study on the refugee population in Thailand, acute infantile beriberi was recognized as the main cause of infant death, accounting for 40% of the infant mortality.[5] The true incidence of infantile Wernicke's encephalopathy is unknown because only a few case reports have been published to date. The majority of rice-eating countries have conquered this disease; however, Kashmir continues to face a thiamine deficiency epidemic because of the lack of awareness of this disease.[7,8] People in Kashmir exclusively eat thoroughly washed milled rice, thus making this population highly susceptible to severe thiamine deficiency. Lactating women are highly prone to thiamine deficiency because of their customary food avoidance practices. Qureshi et al[7] recently published a case series of thiamine-responsive acute life-threatening metabolic acidosis in exclusively breastfed infants from this region. Furthermore, Wani et al[8] reported the MRI findings of infantile encephalitic beriberi, which substantiates the high burden of this fatal disease in this region.

We can measure whole blood TDP levels or erythrocyte transketolase activity (ETKA) for evaluating thiamine levels. Direct TDP measurement in whole blood or erythrocytes using HPLC is a more sensitive and specific index of thiamine nutrition than ETKA measurement.[9,10] Moreover, whole blood TDP levels were drastically low in the 5 patients. Furthermore, a drastic therapeutic response to thiamine supplementation was observed in most of our patients. Therefore, this finding substantiates our observation that the study population was highly thiamine deficient and that therapeutic response to thiamine supplementation is the gold standard for diagnosing acute infantile beriberi.[4,7]

Several inherited metabolic disorders such as organic acidemias, urea cycle defects, and certain disorders of amino acid metabolism are typically associated with acute life-threatening symptoms of encephalopathy.[11] The signs and symptoms appear in a healthy infant with a sudden onset of vomiting, lethargy, and metabolic acidosis, suggesting a differential diagnosis of sepsis but with negative sepsis screen and cultures. In our series, serum ammonia levels measured in 20 patients were within normal limits. In addition, TMS and urine GC-MS analyses of all the 50 patients revealed nonspecific lactic acidemia. Moreover, a rapid therapeutic response to thiamine supplementation makes the diagnosis of inborn errors of metabolism unlikely.

We observed bilateral basal ganglia and thalamic hyperintensity on T2-weighted MRI in 24 patients. In addition, 6 patients exhibited the presence of mammillary bodies and 10 patients had a normal MRI. This group of patients exhibited the typical signs and symptoms of infantile Wernicke's encephalopathy. In a few cases, T2-weighted MRI may be normal; however, in such cases, gadolinium-based contrast MRI may show contrast-enhanced mammillary bodies as the only sign of Wernicke's encephalopathy.[12] Subacute necrotizing encephalopathy (Leigh disease) is a thiamine deficiency-like state in children with similar MRS results and is characterized by a pattern of abnormalities similar to that in Wernicke's encephalopathy, such as a common pathophysiology of mitochondrial damage and laboratory findings of elevated lactate levels. Encephalitis can occasionally lead to symmetric lesions; however, Wernicke's encephalopathy can be distinguished from these disorders by the involvement of mammillary bodies, a highly specific sign of thiamine deficiency,[13] low blood TDP levels, and a rapid therapeutic response to thiamine supplementation.[4,7] This disease is a major public health concern because it contributes to a high percentage of our infant mortality. Health education and thiamine supplementation to the vulnerable population are required immediately to completely eradicate this fatal disease, which is substantially increasing the mortality rate.

In exclusively breastfed infants, we observed acute infantile encephalopathy with epidemiological, clinical, biochemical, and radiological features suggestive of infantile Wernicke's encephalopathy and a favorable therapeutic response to thiamine supplementation during the acute stage. Prompt diagnosis of this condition is essential for optimal outcomes.

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Ethical approval: This study was approved by the Departmental Ethical Committee of SKIMS Srinagar.

Competing interest: None.

Contributors: Bhat JI conceived the study idea and conducted the study. Ahmad QI did the literature search. Ahangar AA analyzed the data and prepared the initial draft of the manuscript. Charoo BA and Sheikh MA provided intellectual inputs in the preparation of manuscript. Syed WA planned the study and supervised the conduct of the sessions. All authors approved the version to be published.

References

1 Sharma S, Mishra D, Aneja S, Kumar R, Jain A, Vashishtha VM, et al. Consensus guidelines on evaluation and management of suspected acute viral encephalitis in children in India. Indian Pediatr 2012;49:897-910.

2 World Health Organization, United Nations High Commissioner for Refugees. Thiamine deficiency and its prevention and control in major emergencies. Geneva: NHD/WHO, 1999.

3 Fattal-Valevski A, Kesler A, Sela BA, Nitzan-Kaluski D, Rotstein M, Mesterman R, et al. Outbreak of life-threatening thiamine deficiency in infants in Israel caused by a defective soy-based formula. Pediatrics 2005;115:e233-e238.

4 Soukaloun D, Kounnavong S, Pengdy B, Boupha B, Durondej S, Olness K, et al. Dietary and socio-economic factors associated with beriberi in breastfed Lao infants. Ann Trop Paediatr 2003;23:181-186.

5 Luxemburger C, White NJ, ter Kuile F, Singh HM, Allier-Frachon I, Ohn M, et al. Beri-beri: the major cause of infant mortality in Karen refugees. Trans R Soc Trop Med Hyg 2003;97:251-255.

6 McGready R, Simpson JA, Cho T, Dubowitz L, Changbumrung S, Böhm V, et al. Postpartum thiamine deficiency in a Karen displaced population. Am J Clin Nutr 2001;74:808-813.

7 Qureshi UA, Sami A, Altaf U, Ahmad K, Iqbal J, Wani NA, et al. Thiamine responsive acute life threatening metabolic acidosis in exclusively breast-fed infants. Nutrition 2016;32:213-216.

8 Wani NA, Qureshi UA, Jehangir M, Ahmad K, Ahmad W. Infantile encephalitic beriberi: magnetic resonance imaging findings. Pediatr Radiol 2016;46:96-103.

9 Herve C, Beyne P, Lettéron P, Delacoux E. Comparison of erythrocyte transketolase activity with thiamine and thiamine phosphate ester levels in chronic alcoholic patients. Clin Chim Acta 1995;234:91-100.

10 Talwar D, Davidson H, Cooney J, St JO'Reilly D. Vitamin B(1) status assessed by direct measurement of thiamin pyrophosphate in erythrocytes or whole blood by HPLC: comparison with erythrocyte transketolase activation assay. Clin Chem 2000;46:704-710.

11 Burton BK. Inborn errors of metabolism in infancy: a guide to diagnosis. Pediatrics 1998;102:E69.

12 Zuccoli G, Pipitone N. Neuroimaging findings in acute Wernicke's encephalopathy: review of the literature. AJR Am J Roentgenol 2009;192:501-508.

13 Kornreich L, Bron-Harlev E, Hoffmann C, Schwarz M, Konen O, Schoenfeld T, et al. Thiamine deficiency in infants: MR findings in the brain. AJNR Am J Neuroradiol 2005;26:1668-1674.

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