Basal Ganglia Disease Mimicking Acute Encephalitis Syndrome Among Infants of Bodo Tribe, Assam

We conducted a review of hospital records of infants with acute encephalitis syndrome with bilateral symmetrical basal ganglia infarcts, between 2011-2015, at a single center in Assam. Thiamine (as part of multivitamin injection) was used in the treatment of 23 infants and not used in 27; Only 1 (3.7%) infant died in the former group and 20 infants (86.9%) died in the latter [RR (95% CI) 0.04 (0.006,0.29); *P*<0.001). Two infants on follow-up had normal development, both in the thiamine group. The study suggests the possibility of subclinical thiamine deficiency, mitochondrial diseases, or *SLC19A3* gene mutation in this population.

Keywords: *Outcome, Thiamine, Vitamin-responsive.*

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Bilateral symmetrical basal ganglia infarcts were observed among infants, who presented with features of acute encephalitis syndrome. Authors believe that patients had good response to multivitamin containing thiamine, and share their experience.

An audit of medical records of children admitted between 2011 and 2015 with a diagnosis of acute encephalitis syndrome with bilateral basal ganglia infarct was conducted at a secondary-level hospital in Tezpur, Assam. Fifty infants had bilateral basal ganglia infarct. Depending on the exposure to multivitamins (thiamine) 27 infants were grouped in the non-exposure group (September, 2011 to April, 2014), and 23 infants in the exposure group (May, 2014 to Sepember, 2015). As thiamine was not separately available, an intravenous multivitamin injection with thiamine was given as a once-a-day infusion during the hospital stay. The constituent was vitamin B1 (thiamine) 100 mg, niacin 100 mg, vitamin B12 1000 mcg, vitamin B2 (riboflavin) 5 mg, vitamin B6 (pyridoxine) 100 mg, d-panthenone 50 mg in 3 mL.

The mean (SD) age at presentation was 6.7 (2.7) months. Common presenting symptoms included seizures (100%), lethargy (90%), fever (70%), and feeding difficulties (76%). There was a preceding illness like fever, lower respiratory tract infection, or acute diarrheal disease in 38 (76%) infants (**Table I**). Laboratory parameters and CSF analysis were unremarkable. Serum lactate was 1.95 mmol/L (normal 0.7-2.1 mmol/L) done for 4 infants in the exposure group. C-reactive protein (CRP) was found to be 3.24 mg/L (normal 0-10 mg/L) done for 5 infants in the exposure group. Japanese encephalitis virus JEV-specific IgM in CSF by IgM-capture ELISA was done for four infants, scrub typhus IgM rapid for six infants, malaria parasite antigen rapid for 20 infants, and automated blood culture and sensitivity for 10 infants, which were all negative. **Web Fig. 1** shows the CT brain of the infants showing bilateral symmetrical infarcts involving the caudate, putamen, globus pallidus, and medial thalamus.

For analysis of outcome, in addition to the infants who died, a moribund child leaving against medical advice was also labelled as death. There were 16 (*n*=27) moribund leave against medical advice infants in the non-exposure group, and 1 (*n*=23) in the exposure group. In the exposure group, 1 (3.7%) infant died, and in the non-exposure group 20 infants (86.9%) died [RR (95% CI) 0.04 (0.006-0.29); *P*<0.001)]. The infants in the exposure group had 96% less risk of death, compared with the non-exposure group. There were subsequent outpatient follow-up data for 7 patients available in the exposure group and none in the non-exposure group. Among them, two infants had normal development, and all others had neurological sequelae. Among the infants with neurological sequelae, two infants were able to walk with support.

Acute encephalitis syndrome (AES) is a public health problem in India, characterized by acute onset of fever, change in mental status with new-onset seizures [1]. Thiamine is successfully used in the treatment of many neurological conditions with basal ganglia involvement like infantile Leigh-like *SLC19A3* gene defect, THTR2 deficiency, biotin thiamine responsive basal ganglia disease [2]. Basal

Table I Characteristics of Children of Bodo Tribe With Acute Encephalitis Syndrome in Assam, 2011-2015 (*N*=50)

	Non-exposure group (n=23)	*Exposure group (n=27)*
Age (mo)[a]	6.8 (2.9)	6.6 (2.8)
Male sex	13 (56.5)	12 (44.4)
Weight for age (z-score <-2)	6 (26.1)	11 (40.7)
Bodo tribe	21 (91.3)	25 (92.6)
Other tribes	2 (8.7)	2 (7.4)
Chief complaints		
Fever	15 (65.2)	21 (77.8)
Cough/coryza/breathing difficulty	8 (34.8)	16 (59.3)
Loose stool/vomiting	3 (13.0)	3 (11.1)
Neurological complaints		
Seizures	23 (100.0)	27 (100.0)
Lethargy	20 (87.0)	25 (92.6)
Feeding difficulties	16 (69.6)	22 (81.5)
Associated Illness		
Respiratory tract Infection	8 (34.8)	14 (51.9)
Acute gastro enteritis	3 (13.0)	3 (11.1)
Management		
Antibiotics	21 (91.3)	23 (85.2)
Acyclovir	2 (8.7)	0 (0.0)
Antipyretics	15 (65.2)	19 (70.4)
Intubated	4 (17.4)	4 (14.8)
Antiseizure medication		
One (Phenytoin)	6 (26.1)	13 (48.1)
More than one	17 (73.9)	14 (51.9)

Data presented in no. (%) or [a]mean (SD). All P>0.05.

ganglia being rich in mitochondria are prone to hypoxia, toxic poisoning, and metabolic, and mitochondrial diseases [3]. Thiamine serves as a cofactor for numerous enzymes, predominantly with mitochon-drial localization. Moreover, the brain is extremely vulnerable to thiamine deficiency due to its dependence on mitochondrial ATP production [3,4]. Furthermore, *SLC19A3* gene mutation is implicated in the deterioration of thiamine transport in neurons via thiamine transporter-2. Depending on the age of the patients, this gene mutation has different clinical pictures. During neonatal period, it presents as Leigh-syndrome-like phenotype, characterized by acute encephalopathy and lactic acidosis. During the early infancy period, presents as a severe disease characterized by epileptic spasms, and bilateral thalamic and basal ganglia lesions [2]. The study suggests the possibility of subclinical thiamine deficiency, mitochondrial diseases, or *SLC19A3* gene mutation in this population.

The present study has a few limitations as it is a single institution experience and a retrospective audit, and has inadequate follow up. Moreover, those who were moribund and left against medical advice were also considered to have died, in addition to 4 deaths that occurred in the non-exposure group and none in the exposure group. Magnetic resonance imaging of brain and extensive metabolic and genetic work up were not performed in the present study. Despite these limitations, our study showed that, multivitamin (thiamine) supplementation may be associated with less risk of death in this group of infants. It raises an important question regarding the status of thiamine deficiency in the affected population. The study provides avenue for future research to explore the possible cause of thiamine responsiveness in acute encephalitis syndrome in the Bodo tribal community of Assam. We feel that multivitamin (thiamine) supplementation could be considered in the management protocol in infants with AES and symmetrical basal ganglia involvement.

Ethics approval: Approved by Emmanuel Hospital Association Institutional Ethics Committee (No. 233; 22-07-2020) dated July 22, 2020.
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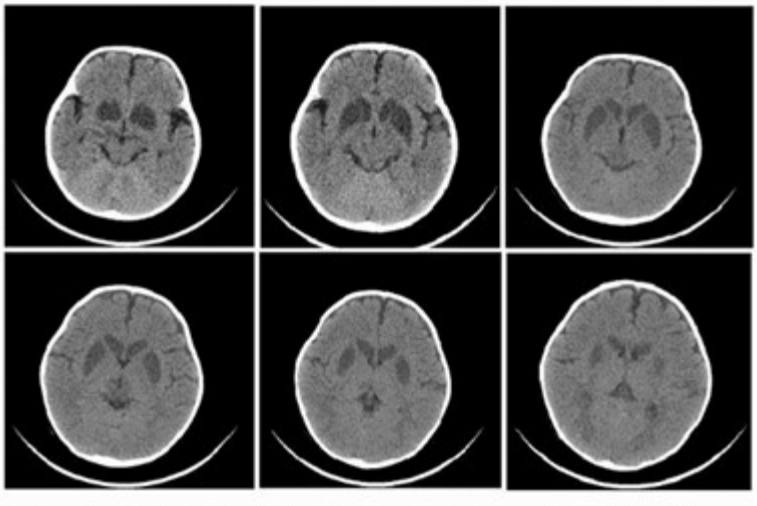

Web Fig. 1 CT Brain showing bilateral basal ganglia infarcts.