Thiamine Deficiency and Cardiac Dysfunction in Cambodian Infants

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Objectives To compare blood thiamine concentrations, echocardiography findings, and plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in infants with clinically diagnosed beriberi and healthy matched controls, and to evaluate changes after thiamine treatment.

Study design Sixty-two Cambodian infants (20 cases and 42 controls), aged 2-47 weeks, were enrolled in this prospective study. Echocardiography and phlebotomy were performed at baseline and after thiamine treatment.

Results Both cases and controls were thiamine-deficient, with median blood thiamine diphosphate (TDP) concentrations of 47.6 and 55.1 nmol/L, respectively (P = .23). All subjects had normal left ventricular ejection fraction. The median NT-proBNP concentration in cases (340 pg/mL [40.1 pmol/L]) was higher than previously reported normal ranges, but not statistically significantly different from that in controls (175 pg/mL [20.7 pmol/L]) (P = .10), and was not correlated with TDP concentration (P = .13). Two cases with the lowest baseline TDP concentrations (24 and 21 nmol/L) had right ventricular enlargement and elevated NT-proBNP levels that improved dramatically by 48 hours after thiamine administration.

Conclusion Only a minority of thiamine-deficient Cambodian infants demonstrate abnormal echocardiography findings. Thiamine deficiency produces echocardiographic evidence of right ventricular dysfunction, but this evidence is not apparent until deficiency is severe. NT-proBNP concentrations are mildly elevated in sick infants with normal echocardiography findings, indicating possible physiological changes not yet associated with echocardiographic abnormalities. *(J Pediatr 2014;164:1456-61)*.

Wet beriberi, a disease caused by thiamine deficiency, is a common diagnosis in parts of Southeast Asia.[1,2] Thiamine deficiency is widespread among nursing mothers and their breast-fed infants in Prey Veng Province, Cambodia. Mothers in this region efficiently absorb oral thiamine and secrete it in breast milk, but they consume only approximately one-half of the recommended daily intake of thiamine, implicating maternal dietary inadequacy as the cause of infant thiamine deficiency.[3-5] Further studies in this area of Cambodia found that up to one-half of deaths during the first year of life may be attributable to beriberi, but that both infants with a clinical diagnosis of beriberi and apparently healthy matched control infants have low thiamine diphosphate (TDP) concentrations.[4,6] This implies that thiamine deficiency, as defined by reference ranges for US children with thiamine deficiency, is not necessarily sufficient to cause wet beriberi.

The clinical diagnosis of wet beriberi is made when signs of congestive heart failure are present (tachypnea, tachycardia, wheezing, hepatomegaly), often with dysphonia, and the child improves after receiving thiamine.[7] Autopsy data from infants with wet beriberi show right ventricular (RV) dilation and hypertrophy, with relative sparing of the left ventricle.[8,9] The few available reports on echocardiography in infants with wet beriberi describe tricuspid regurgitation, right heart dilation, and pulmonary hypertension that resolved after thiamine therapy.[10,11] No previous studies have correlated echocardiographic assessment with blood thiamine or plasma N-terminal pro-B type natriuretic peptide (NT-proBNP) concentrations in children with beriberi.

The specific aims of the present study were: (1) to use portable echocardiography to compare cardiac function in infants with clinical signs of wet beriberi and apparently healthy control infants; (2) to evaluate cardiac changes in infants with clinically diagnosed beriberi over the first 48 hours of treatment; and (3) to correlate echocardiographic findings and NT-proBNP levels with case-control status and blood thiamine concentrations.

ETK	Erythrocyte transketolase
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro-B type natriuretic peptide
RV	Right ventricular
TDP	Thiamine diphosphate

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Methods

Infants aged 2-47 weeks (n = 62) were enrolled in this prospective, observational study at the Svay Chrum clinic in the Mesang District of Prey Veng Province, Cambodia, between July 10, 2012, and August 3, 2012. All infants presenting to the clinic were screened for clinical findings of beriberi, and 20 met the study criteria. In addition, 42 control infants deemed healthy by their mothers were recruited from surrounding villages. Informed consent was obtained from all mothers. A survey was administered to mothers of all enrolled infants to elicit information on environmental and dietary exposures, as described previously.[4] All infants underwent echocardiography and phlebotomy at enrollment. Infants with clinical beriberi received thiamine and underwent repeat echocardiography at 24 and 48 hours after presentation, as well as repeat phlebotomy at 48 hours, before the third daily thiamine administration. Ethics approval was obtained from the Mayo Clinic's Institutional Review Board and from the Cambodian National Ethics Committee for Health Research.

Infants were defined as having clinical beriberi who met all of the following criteria: hepatomegaly (liver edge ≥2 cm below the costal margin), respiratory rate ≥40/min, heart rate ≥140/min, and temperature <37.5°C. Infants with a heart rate >170/min or respiratory rate >70/min (necessitating immediate intervention), and those who had received thiamine treatment at any time since birth, were excluded from the study. This clinical definition was used in a previous study of infant beriberi in Cambodia and is a more specific derivation of the major criteria cited in the literature.[1,2,4,7,8,11] Healthy control infants with tachypnea (>50 breaths/min), tachycardia (>150 beats/min), or a temperature >37.5°C were excluded. Enrolled healthy control infants were matched to infants with beriberi by sex and age (±2 weeks for infants aged <2 months and ±1 month for older infants). More control infants than sick infants were enrolled, because controls were enrolled synchronously and matched to cases at the conclusion of the study. All cases had at least 1 match by the foregoing criteria, and a second match was added when possible.

Echocardiography was performed using a portable SonoSite M-Turbo ultrasound machine (SonoSite, Bothell, Washington). Standard parasternal long-axis, parasternal short-axis, apical 4-chamber, and subcostal images were obtained and stored digitally for later analysis. A total of 3 mL of blood was collected at each phlebotomy. Hematocrit was measured immediately. Because of logistical factors, samples from sick infants were frozen to −20°C within 20 minutes, whereas samples from healthy control infants were placed on ice within 2 minutes and frozen to −20°C within 4 hours. All specimens were transferred on dry ice to a −70°C freezer at the National Institute of Public Health in Phnom Penh, Cambodia within 2 weeks of collection. Frozen specimens were batch-shipped to ARUP Laboratories, Salt Lake City, Utah, in a Cryoport Dry Vapor Shipper (www.cryoport.com) at −70°C and were thawed immediately before the thiamine assay, performed within 3 months of collection.

Given this study's observational nature, treatment of sick infants was determined by the local health practitioners. Immediately after the initial echocardiographic examination, all patients with clinical beriberi received 100 mg of thiamine intramuscularly, divided into 3 doses delivered over 90 minutes. This treatment was repeated at 24 and 48 hours after presentation, in accordance with local protocol.

Plasma thiamine, thiamine monophosphate, and whole blood TDP assays were performed by high-performance liquid chromatography as described previously.[12] The adult reference interval (derived from self-reported healthy US adults) is 8-30 nmol/L for total plasma thiamine (plasma thiamine + thiamine monophosphate) and 70-180 nmol/L for whole blood TDP. Pediatric thiamine reference ranges have not been formally established, but published TDP concentrations for healthy US infants fall within or above the adult reference range.[4,13] NT-proBNP measurements were performed on a Roche Cobas e411 unit (Roche, Basel, Switzerland) as described previously.[14] NT-proBNP reference ranges remain ill-defined in the normal pediatric population, but an upper limit of normal has been reported as 299-348.6 pg/mL (35.3-41.1 pmol/L) for infants aged 4 months to 1 year.[15,16] Sahin et al[17] and Nevo et al[18] have proposed cutoff values for cardiac dysfunction screening of 514 pg/mL (60.7 pmol/L) and 415 pg/mL (49 pmol/L), respectively. A subset analysis of healthy neonates aged 1-5 days found a mean NT-proBNP of 1937 pg/mL (228.6 pmol/L), implying an age-related drop after the first few days of life.[19]

Digital echocardiography clips were stored electronically and subsequently analyzed by 2 independent reviewers (R.L. and A.C.) blinded to patient status. The following measures were assessed: left ventricular (LV) end-diastolic diameter, LV end-systolic diameter, degree of tricuspid regurgitation (trivial, mild, moderate, or severe), visual assessment of RV size (normal, borderline, mild, moderate, or severely increased), and the presence/absence of pericardial effusion. Visual assessment of RV systolic function (normal, mild, moderate, or severe reduction) was performed using qualitative data from all acoustic windows, as specified by the American Society of Echocardiography.[20] LV ejection fraction (LVEF) was calculated according to standard methods (normal range), and LV dimensions were indexed to body surface area.

Data were recorded as mean ± SD, median (range), or number (%) per group, as appropriate. To account for matching by age and sex, statistical comparisons between study groups were made with conditional logistic regression. Baseline variables were presented as median and range for each study group and were compared between study groups with conditional logistic regression. The impact of thiamine on cardiac function and vital signs in sick infants was assessed by measurements obtained at baseline and after 2 days, using the Wilcoxon signed-rank test or McNemar test as appropriate. Both LVEF and NT-proBNP were compared with