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Thiamine Deficiency in Cambodian Infants with and without Beriberi

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Abstract

Objectives—To test the hypothesis that heavy metal toxicity and consumption of thiaminase-containing foods predispose to symptomatic thiamine deficiency.

Study design—In a case-control study, thiamine diphosphate (TDP) blood concentrations were measured in 27 infants diagnosed with beriberi at a rural clinic, as well as their mothers and healthy Cambodian and American controls. Blood and urine levels of lead, arsenic, cadmium, mercury, and thallium were measured. Local food samples were analyzed for thiaminase activity.

Results—Mean TDP level among cases and Cambodian controls was 48 and 56 nmol/L, respectively ($P = .08$) and was 132 nmol/L in American controls ($P < .0001$ compared with both

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Cambodian groups). Mean TDP level of mothers of cases and Cambodian controls was 57 and 57 nmol/L ($P = .92$), and was 126 nmol/L in American mothers ($P < .0001$ compared with both Cambodian groups). Cases (but not controls) had lower blood TDP levels than their mothers ($P = .02$). Infant TDP level decreased with infant age and was positively associated with maternal TDP level. Specific diagnostic criteria for beriberi did not correlate with TDP level. There was no correlation between heavy metal levels and either TDP level or case/control status. No thiaminase activity was observed in food samples.

Conclusions—Thiamine deficiency is endemic among infants and nursing mothers in rural southeastern Cambodia and is often clinically inapparent. Neither heavy metal toxicity nor consumption of thiaminase-containing foods account for thiamine deficiency in this region.

Beriberi is rarely seen in developed countries but is endemic in parts of Southeast Asia,¹ and is a major cause of neonatal mortality in some Asian populations.^{2–5} The accepted cause of beriberi in breastfed infants is maternal thiamine deficiency. Beriberi has been associated with lower socioeconomic class and traditional rice preparation methods, including use of polished rice (from which the thiamine-rich bran has been removed) and non-parboiled rice.⁵ Thiamine antagonists in coffee, tea, and betel nut, as well as thiaminases in fermented fish may block thiamine absorption or bioavailability.⁶ There is some evidence that heavy metals decrease bioavailability of thiamine, and that thiamine deficiency potentiates intestinal absorption of heavy metals.^{7–10}

Infantile beriberi is often diagnosed clinically in the Mesang District of Prey Veng Province, in southeastern Cambodia. These infants typically present with signs of heart failure, including hepatomegaly, tachypnea, tachycardia, and dysphonia (a distinctive hoarse cry that may progress to aphonia), and improve rapidly following thiamine administration. However, the association between the clinical diagnosis of beriberi and blood thiamine levels is unknown in this region. Our specific aims were to determine whether clinically diagnosed beriberi was actually associated with thiamine diphosphate (TDP) deficiency, and whether heavy metal toxicity or other environmental or dietary factors were associated with clinical illness or blood TDP concentrations. The traditional laboratory method of determining thiamine deficiency is a functional assay for the thiamine-dependent erythrocyte transketolase enzyme,^{2,11} which may be influenced by factors other than thiamine deficiency.¹² We measured TDP levels directly in sick infants and their nursing mothers, as well as in both Cambodian and American controls.

Methods

Mothers of infants with a clinical diagnosis of beriberi presenting to Svai Chrum Clinic, Mesang District in Prey Veng Province, Cambodia (latitude 11.374364, longitude 105.564183, a non-malarious area) were invited to participate. We enrolled 27 cases and their mothers, 27 healthy Cambodian control infants and their mothers residing in the same district, and 20 healthy American control infants and their mothers residing in Olmsted County, Minnesota. The study was approved by the Cambodian National Ethics Committee for Health Research and the Mayo Clinic institutional review board.

Beriberi was defined as hepatomegaly (liver edge >2 cm below the right costal margin), respiratory rate >40, heart rate >140, absence of fever, and at least 2 of the following: (1) aphonia or dysphonia; (2) wheezing on exam; (3) decreased urine output; (4) recent vomiting or spitting up; and (5) increased irritability. Infants with a respiratory rate >70 breaths per minute or a pulse >170 beats per minute were excluded to avoid delays in treatment. Inclusion criteria included maternal age >18 years and infant age >7 months. Exclusions for controls included previous infant hospitalization, transfusion, or recent symptoms requiring evaluation. Control infants were matched to cases by sex and age (± 2 weeks if <1 month of age, otherwise ± 1 month). Cases were treated with 3 doses of thiamine (25, 25, then 50 mg) administered 30 minutes apart and repeated on the subsequent 2 days, and mothers received a 30-day supply of multivitamins.

Blood and urine were collected from all Cambodian infants and their mothers. Hematocrit was measured immediately. Specimens were immediately placed on ice, frozen at -40°C within 30 hours of collection, and flown to the United States on dry ice. Heparinized whole blood was assayed for TDP. Urine and blood were assayed for mercury, arsenic, cadmium, thallium, and lead. Laboratory assays were performed at Mayo Clinic in Rochester, Minnesota within 30 days of specimen collection. Blood obtained from American control infants and their mothers was assayed for TDP.

Maternal diet was quantified using a standardized food frequency questionnaire, and mothers were surveyed regarding drinking water source, use of topical lotions, and intake of alcohol, fish paste, fish sauce, monosodium glutamate, salt, snack foods, chewing tobacco, and betel nut. Daily maternal thiamine intake was estimated using a published table of food thiamine content.¹³

Food samples for thiaminase assays were collected from local markets, and included dried leaves, roots, and bark (baat ptul, wadakuen, beetle nut leaves, buffalo horn tree, roots of the ropheak bush, gamthea, bark of skew tree, mekong tree, ktum branch, and sang tree), palm sugar, fish paste, and soy sauce.

TDP and metal assays were performed at Mayo Medical Laboratories in Rochester, Minnesota. TDP was measured¹⁴ in heparinized whole blood samples by high performance liquid chromatography, as previously described.¹⁵ The reference range in our lab for TDP in adults is 80–150 nmol/L whole blood or, when divided by hematocrit expressed as a decimal, (thiamine diphosphate divided by hematocrit [TDP/Hct]), 150–290 nmol/L red blood cells. A TDP reference range for infants has not been established in our lab, but should be higher than for adults.¹⁶ Metals were quantified in blood and urine as previously described.¹⁷

Thiaminase assays were performed at Texas A&M University in College Station, Texas, using previously described methods.^{18,19} Thiaminase activity was measured in supernatant of liquid or freshly suspended ground solid samples. Reaction mixtures, as well as appropriate positive controls containing *Bacillus thiaminolyticus* thiaminase I, were assayed for thiamine by reverse-phase high performance liquid chromatography.

Data were analyzed using JMP 8 software (SAS Institute, Cary, North Carolina). Dichotomous variables were compared by the χ^2 test or Fisher exact test. Normally distributed continuous data were compared by Student *t* test or paired *t* test. The association of findings with TDP level was assessed with the Wilcoxon rank-sum test. Linear regression was used to predict infant TDP and TDP/Hct using either age or maternal values by study groups.

Results

Median age of beriberi cases, Cambodian controls, and American controls was 105 days (range 26–209), 107 days (17–226), and 113 days (18–203); 96% of cases and Cambodian controls and 85% of American controls were breastfed; 19% of cases and 22% of Cambodian controls received solid foods, and 35% of American controls received solid food or formula.

Thiamine Concentrations

The mean blood TDP concentration in beriberi cases, Cambodian infant controls, and American infant controls was 48 (95% CI: 40, 56), 56 (95% CI: 46, 65), and 132 (95% CI: 112, 151) nmol/L whole blood, respectively ($P = .08$ for comparison between Cambodian cases and controls, $P < .0001$ for comparison between American controls and both Cambodian groups; Figure 1). The mean blood TDP concentration in Cambodian mothers of cases and controls and American control mothers was 57 (95% CI: 51, 64), 56 (95% CI: 46, 65), and 126 (95% CI: 113, 138) nmol/L, respectively ($P = .92$ for comparison between Cambodian cases and controls, $P < .0001$ for comparison between American and both Cambodian groups); 94% of Cambodian mothers had TDP levels of <80 nmol/L. The 1 Cambodian mother who used a multivitamin had a TDP level of 101 nmol/L, and her infant's TDP level was 90 nmol/L. Mean TDP/Hct of cases and Cambodian infant controls was 135 (95% CI: 114, 157) and 159 (95% CI: 133, 184) nmol/L red blood cells, respectively ($P = .08$), and of their mothers 141 (95% CI: 126, 158) and 150 (95% CI: 134, 166) respectively ($P = .46$).

Infant TDP concentration was inversely proportional to infant age among cases but not Cambodian or American controls (Figure 2). Infant TDP levels were proportional to maternal TDP levels among beriberi cases and both Cambodian and American controls (Figure 3). Analyses substituting TDP/Hct for TDP gave similar results. Cases had lower blood TDP levels than their mothers ($P = .02$) but this was not true of Cambodian or American controls ($P = .78$ and $.46$ respectively). No components of the beriberi case definition were associated with blood TDP or TDP/Hct concentrations in univariate analysis (P values ranged from $.12$ – $.98$).

Cambodian infant cases and controls had a mean hematocrit of 35% (95% CI: 33, 37) and 35% (95% CI: 31, 39). The mean hematocrit in Cambodian mothers of cases and controls was 41% (95% CI: 38, 44) and 38% (95% CI: 34, 42), respectively.

Of the multiple dietary and environmental risk factors for thiamine deficiency that were assessed, inclusion of solid foods in the infant's diet ($P = .001$) and use of a topical ointment

("Tiger Balm") containing camphor, menthol, and methyl salicylate ($P = .018$) were associated with lower infant TDP concentrations in univariate analysis.

Response to Thiamine Therapy

All beriberi cases improved after thiamine administration. Sixteen also received antibiotics. Improvement was rapid by individual clinical assessment, but no infant had a decrease in the extent of palpable liver of 1 cm by 24 hours; at 72 hours, 20% demonstrated this decrease in liver size. The respiratory rate decreased by 10 breaths per minute in 26% by 24 hours and in 38% by 72 hours. Heart rate decreased by 20 beats per minute in 30% by 24 hours and in 33% by 72 hours. Mean baseline TDP blood level of infants with and without objective findings of improvement at 24 hours was 48 nmol/L (95% CI: 35, 61) and 48 nmol/L (95% CI: 36, 60) ($P = .82$); corresponding TDP/Hct levels were 134 (95% CI: 98, 170) and 136 (95% CI: 106, 166) ($P = .92$).

Heavy Metal Concentrations

As shown in the Table, arsenic and mercury levels were normal in Cambodian infants, and were mildly elevated in some mothers, likely due to fish consumption.²⁰ Elevated blood lead levels (10–41 mcg/dL) were found in 15% of Cambodian infants (4 cases and 4 controls). There was no correlation between arsenic, lead, cadmium, or thallium levels and blood TDP levels. Infants with higher blood mercury levels had higher TDP levels; however no infant had an elevated blood mercury level.

Maternal Thiamine Intake and Thiaminase Activity in Local Foods

Cambodian maternal thiamine intake was estimated to be 0.75 mg/d (cases) and 0.85 mg/d (controls). Only 4% of nursing Cambodian mothers met the recommended intake of 1.5 mg/d.²¹ Antepartum and/or postpartum food avoidance was reported by 60% of Cambodian mothers, usually for certain vegetables, duck meat, or buffalo meat. There was no association between maternal food avoidance and either TDP or TDP/Hct levels of mothers or infants. No food-dependent degradation of thiamine was observed in local foodstuff samples under conditions where thiamine was completely consumed in the presence of only 10 nM recombinant thiaminase.

Discussion

Beriberi is an important cause of infant morbidity and mortality in developing Asian countries where the dietary staple is polished rice.^{1,2,4,5} We sought to ascertain whether infants presenting with the cardinal signs and symptoms of beriberi to a rural clinic in southeastern Cambodia were deficient in thiamine, and whether heavy metal toxicity, maternal diet, or other environmental factors were contributing. We found that thiamine deficiency appears to be commonplace among Cambodian mothers and infants, and is likely due to dietary insufficiency rather than heavy metal toxicity or thiaminases in food.

Our most important finding was low blood TDP levels among Cambodians compared with matched American controls. Most Cambodian mothers were thiamine deficient and had insufficient thiamine in their diet. Cambodian infant cases and controls had markedly lower

TDP levels than American control infants. There is evidence that phosphorylated thiamine levels (measured with a different assay) are high in thiamine-replete American infants, declining to normal adult ranges after the first year of life.¹⁶ Our data thus suggest that most Cambodian infants we studied were thiamine deficient. Thiamine deficiency appears to be endemic among infants and nursing mothers in this region of rural Cambodia, echoing results of studies from Thailand and Laos of postpartum mothers⁴ and hospitalized infants without clinical signs of beriberi.²

Older Cambodian cases had lower TDP levels than younger cases, presumably because mothers who were thiamine deficient nursed them. Sick infants also had significantly lower thiamine levels than their mothers, but this was not true for either Cambodian or American controls. It is unclear whether acute infection,²² differences in excretion of thiamine in breast milk, or variations in infant absorption, metabolism, and excretion of thiamine may have been the cause of this finding.

Our results suggest that the traditional diagnostic criteria for infantile beriberi may be nonspecific for diagnosis of thiamine deficiency in an endemic region. We were unable to identify presenting signs and symptoms that correlated with initial blood TDP levels. Acute infectious illnesses are common in infants and, although often accompanied by fever, could present in similar fashion to beriberi. Severity of infectious illnesses is likely magnified by underlying thiamine deficiency, and acute infections may precipitate previously latent beriberi.^{5,11,22} We saw rapid improvement following thiamine administration, as expected in beriberi,⁵ but this was not accompanied by quick resolution of hepatomegaly or normalization of vital signs. In a setting where thiamine deficiency is widespread and implicated as a leading cause of death,²³ liberal administration of thiamine to sick infants is justified.

The Cambodian infants whose diet was supplemented with solid foods were more likely to be thiamine deficient. Foods previously reported to contain thiaminase activity (fermented fish paste) or thiamine antagonists (tea, betel nut)²⁴ were not associated with lower thiamine levels in this study. Mothers cooked their fish paste prior to consumption, which could result in heat-denaturation of the thiaminase.²⁵ No significant thiaminase activity was observed in any of the local food samples tested. Mildly elevated maternal mercury and arsenic levels were likely due to fish consumption, and were not associated with low TDP levels in this cohort.

The results of this study are limited by the small sample size and lack of an infant reference range for TDP in our lab. However, the findings suggest that thiamine deficiency is prevalent in mothers and both symptomatic and apparently healthy children in Prey Veng Province of southeastern Cambodia. Further research is needed in order to understand the interplay between clinical findings, blood thiamine levels, disease severity, and final diagnosis in children with suspected beriberi. Research is also required to identify effective and appropriate methods of supplementing thiamine in pregnant and nursing Cambodian women.

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Glossary

TDP	Thiamine diphosphate
TDP/Hct	Thiamine diphosphate divided by hematocrit

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Figure 1.

Whole blood TDP concentrations in Cambodian and American subjects (nmol/L). *Boxes* IQR; the lines inside the boxes indicate median values. *Whiskers* represent the range of non-outlier values outside of the IQR, with outliers indicated by *open circles*. There were no significant differences between Cambodian cases and controls; $P < .0001$ for 3-way ANOVA for both infants and mothers.

Figure 2. Relationship between infant whole blood TDP concentration and infant age. P values are for the slope in each of 3 separate linear regressions.

Figure 3.

Relationship between infant whole blood TDP concentration and maternal whole blood TDP concentration. P values are for the slope in each of 3 separate linear regressions. The null hypothesis of slope = 1 corresponds to the same rate of increase for infants and mothers.

Table

Heavy metal levels in Cambodian infants and mothers

Association with infant's TDP level (<i>P</i> -value)				
	Normal range	Mean infant level (range)	Mean maternal level (range)	
				Infant metal level
				Maternal metal level
Whole blood				
Lead	<4 mcg/dL	7 (1–41)	5 (2–9)	.72
Arsenic	<5 ng/mL	<5 (5)	<5 (5)	.50
Cadmium	<4.9 ng/mL	0.2 (0.2)	0.5 (0.2–2.1)	.90
Mercury	<10 ng/mL	4 (2–9)	6 (3–16)	.0005*
Thallium	<1 ng/mL	<1 (<1)	<1 (<1)	1.0
Urine				
Lead	<10 mcg/L	6.0 (5–24)	5.1 (5–8)	.29
Arsenic	<35 mcg/L	<15 (<15)	57 (15–172)	1.0
Cadmium	<1.3 mcg/L	0.2 (0.2)	0.4 (0.2–1.8)	1.0
Mercury	<10 mcg/L	<1.0 (<1.0–1.0)	1.5 (<1–11)	1.0
Thallium	<1 mcg/mL	<1 (<1)	<1 (<1)	1.0

* Increased mercury levels in infants were significantly associated with higher TDP levels.