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Beri-beri: the major cause of infant mortality in Karen refugees

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Abstract

During a prospective evaluation of malaria prophylaxis in pregnancy in a refugee population on the north-western border of Thailand from 1987 to 1990, an extremely high infant mortality rate (18%) was documented despite good access to health care. Infantile beri-beri was recognized as the main cause of death accounting for 40% of all infant mortality. Thereafter, severe vitamin B_1 deficiency in infants was diagnosed and treated promptly. The impact of this was assessed prospectively from 1993 to 1996 in a second cohort study. The case fatality of infantile beri-beri fell from almost 100% to 7%. The overall infant mortality rates declined from 183 to 78 per 1000 live births. Post-neonatal deaths fell by 79% (95% CI 65–87%) while neonatal mortality remained unchanged. Mortality resulting from acute respiratory infections did not change (15 and 11 per 1000, respectively), whereas mortality attributable to beri-beri decreased from 73 to 5 per 1000 ($P < 0.0001$). Before its recognition approximately 7% of all infants in this population died from infantile beri-beri. This lethal but preventable syndrome may be more common than hitherto recognized, particularly in refugee populations, in this populous region.

Keywords: beri-beri, nutrition, vitamin B_1, children, refugee health, Thailand

Introduction

The mortality rate of infants born in remote communities living in tropical areas of the world is often high. Respiratory infections and diarrhoeal diseases claim most of these lives (Greenwood, 1999; Bhan, 2000). Improvements in health care usually lead to a reduction of infant mortality (Lamb *et al.*, 1984; Hearst, 1985; Bang *et al.*, 1990; Pandey *et al.*, 1991). On the north-western border of Thailand, there are a series of camps for displaced persons of the Karen ethnic minority. This population currently totals approximately 120 000. Food and health care, including antenatal clinics, hospital, and an immunization programme, were provided by non-governmental organizations from the beginning of the influx of people in 1984. Despite ready access to health care facilities, the infant mortality rate remained over 20% which is amongst the highest ever recorded. Elsewhere such high mortalities are associated with extreme poverty and absence of health care. However, respiratory infections and diarrhoeal diseases, the 2 main causes of infant death in deprived populations, did not appear to be major causes of mortality. We present evidence that in this area infantile beri-beri was the major killer of infants.

Methods

Study area and background

Since their arrival in 1984, displaced persons of the Karen ethnic group have settled in camps of various sizes (1500–30 000 inhabitants) situated along the western border of Thailand. Health care was provided throughout by Médecins Sans Frontières (MSF). From the outset multidrug-resistant malaria was the major public health problem. Malaria control was based upon early diagnosis and effective treatment (Nosten *et al.*, 1987). Thus, dispensaries with laboratories were established in all camps at a walking distance from any house. In-patient departments and small hospitals were built in camps with more than 2000 inhabitants. Each health structure was run by local health workers and expatriate staff visited them daily. Until 1996, in the 2 largest camps, Shoklo (8000 inhabitants) and Maela (then 21 000), expatriate physicians were on call throughout the day and night. In these camps, there were also health structures (dispensaries and small hospitals) run by the Shoklo Malaria Research Unit (SMRU). Although the primary objective of this health system was malaria control, all health structures were able to treat the most common presenting conditions, such as respiratory infections and diarrhoeal episodes. Antenatal clinics were established in 1986. Infants were seen monthly and immunized following the Expanded Programme of Immunization (EPI) recommendations. In this population the level of literacy was relatively high (70%) and the health structures were well utilized. Nearly all (90%) pregnant women in the camps attended the antenatal clinics and the immunization coverage was high (90% for diphtheria–pertussis–tetanus–poliomyelitis; 70–80% for measles).

When it became clear during the course of prospective studies of malaria in pregnancy that there was an unusual and large peak of infant mortality at approximately 3 months of age, an infectious aetiology was sought initially but not found. Infantile beri-beri was recognized as a major cause of infant death in 1990 (Nosten *et al.*, 1994). This was surprising as wet and dry beri-beri were rare in adults in this population. Local health workers were then trained to give an i.m. injection of vitamin B_1 to any infant who presented with a sudden onset of respiratory distress or shock. No other specific treatments were given systematically. Pregnant women with clinical signs compatible with thiamine deficiency (principally peripheral paraesthesiae) were given a daily dose of 100 mg of thiamine hydrochloride until delivery. During the lactating period, until 9 months post-partum, women and their babies were followed at MSF clinics and received 10 mg of thiamine hydrochloride a week and a food supplement (see below).

Diet during the study period

Food was provided by a consortium of charities. In the first years following their arrival, the refugees were living in open camps and were able to work outside in Thai farms or to go back to their own farms in Burma (Myanmar). Some refugees also grew green vegetables and kept poultry (mainly for egg production) in the camps. The ration distributed by the charities comprised polished rice (550 g/d), salt (8 g/d) and fermented fish paste (28 g/d). This ration was considered as a complement. It was not the full standard ration in terms of quality and quantity that is recommended in a

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refugee situation where other food is not available. However the dietary contribution of the other sources of food (vegetables and poultry in the camps; food bought by cash obtained from outside work; farming in Myanmar) was not known and was likely to be unevenly distributed among the refugees.

In 1992, a survey was conducted by MSF (Le Bihan, 1992) in order to estimate the nutritional content of the daily ration in lactating women. A standardized questionnaire was given to 215 lactating women with a baby aged 1–6 months. Their usual behaviour regarding the frequency, methods of preparation and contents of meals, and consumption of thiaminase-containing foods, were all assessed. In addition a 24 h recall method was used for the estimation of the quantity and quality of the ration. The results were compared to general and Thai recommended dietary allowances (Ministry of Public Health, Thailand, 1989; National Academy of Sciences, USA, 1989). The survey concluded that the daily energy input was 2000 kcal comprising 89% of carbohydrates. The thiamine content was estimated to be between 0.55 and 0.75 mg/d and was therefore about half of the recommended input (0.5 mg/1000 kcal with a minimum of 1 mg/d and a supplement of 0.4 mg/d during pregnancy and lactation). Less than 10% of the subjects were eating meat or leguminous plants once or more each week; 11% ate one or more eggs and 18% had dry fish once a week. In addition, 79% of the women chewed betel nuts (which contain a well-characterized thiaminase) every day, and most of them (92%) did this less than 1 h after a meal.

After recognition of the infantile beri-beri syndrome, all pregnant women were given a supplementary food ration (500 g soybeans and 4 eggs/week). In 1995, after some of the camps were attacked, the refugees were relocated in large, closed camps. They became more dependent on the food given by charities and further nutritional supplements (such as cooking oil) were added to their ration.

Another survey, conducted in 1997, gave results generally similar to those of the 1992 survey. The nutritional content of the ration supplied nearly adequate energy (2100 kcal/d during pregnancy) and protein, but was still low in micronutrients, such as vitamin A, vitamin C, folate and thiamine (Nutrition Incorporated, 1997).

Study populations

From 1987 to 1990 (i.e. before recognition of the high infant mortality and its relationship to thiamine deficiency), a cohort of 287 infants born to mothers who participated in a trial of antimalarial prophylaxis was followed from birth to 1 year of age (cohort I). The objective of this study was to assess the safety and efficacy of mefloquine (Nosten *et al.*, 1994). A second cohort (II) of 1495 infants born between 1993 and 1996 was followed in order to describe the effects of maternal malaria on infant survival (Luxemburger *et al.*, 2001). Study procedures were similar in the 2 cohorts on admission and for data collection regarding mortality.

All pregnant women were enrolled at their first consultation at the antenatal clinics, after they gave informed consent. On admission, information was obtained retrospectively about maternal demographic data, past obstetric history and past malaria history. Pregnant women were then followed weekly. Malaria episodes were treated each time they were detected irrespective of the presence or absence of symptoms. Iron and folic acid treatments were given to all women who became anaemic, defined as a haematocrit < 30%. Haematinics were continued until delivery. All women were encouraged to deliver in hospital. When they delivered at home, home visitors brought the babies to the clinic within 3 d. The newborn infants were weighed (Salter® scale; accurate to the nearest 50 g). Low birthweight (LBW) was defined as a birthweight under 2500 g. Infants were then followed monthly until 1 year of age. In this setting, most of the children who die in infancy presented to the dispensary in their final illness and a large proportion of deaths occurred in hospital. The cause of death was determined by agreement of 2 physicians who either managed the child or studied the dispensary and/or hospital records. When deaths occurred at home, the mothers were interviewed by the investigators.

Study procedures differed between the 2 cohorts for the collection of morbidity data during infancy. Morbid events were detected passively in cohort I (i.e. each time the child came to the SMRU dispensary). In cohort II active detection of each morbid event was done. Mothers were encouraged to bring their babies to the Unit's dispensary for any illness. Consultations in MSF health structures were also recorded. Infants were seen weekly at home by home visitors who cross-checked that the babies had been seen by a health worker in case of illness. This systematic follow-up was implemented because cohort II was much larger than cohort I and was conducted in several camps. However, the women in cohort I were living in 2 camps in close proximity to the research unit, and used the medical services extensively. It is highly likely that any important morbid events would have been reported.

Data analysis

The data were analysed by Epi Info 6.0 (CDC, Atlanta, GA, USA). Dichotomous variables were compared by the χ^2 test with Yates's correction or Fisher's exact test. Normally distributed continuous data were compared by Student's t and data that were not normally distributed by the Mann–Whitney U test.

Results

Clinical presentation

The usual clinical presentation of the lethal syndrome attributed to vitamin B_1 deficiency was the sudden onset of shock in a previously well-nourished breastfed baby of 2–3 months of age. The mother usually described a change in the baby's cry to a hoarse weak cry over the preceding days, with reluctance to feed, sometimes vomiting, and then a relatively sudden onset of respiratory distress. A preceding infection occurred in some cases. Five of the first 10 well-documented cases had attended the dispensary 1–3 d before death. Usually this was for a mild upper respiratory tract infection, which was treated with antibiotics in the outpatient department. In other cases the mother did not report any previous illness. Further questioning of the mother sometimes revealed a history of intermittent paraesthesiae in the hands and feet during and after pregnancy without subjective or clinical evidence of neurological deficit. On examination the baby would usually be of normal weight and development, apyrexial, pale, clammy, with rapid shallow breathing, poor peripheral perfusion, and low or unrecordable blood pressure. There was no peripheral oedema and no obvious neurological abnormalities. The liver, but not the spleen, was usually enlarged. Despite all resuscitation attempts the children would usually die within minutes or hours. Following recognition of the syndrome, i.m. thiamine (50 mg) was given to all cases, and most babies recovered within 6 h, often accompanied by significant diuresis. This dramatic clinical response to parenteral thiamine and no other intervention was considered diagnostic of infantile beri-beri.

Cohorts

Baseline characteristics of the 2 cohorts are summarized in the Table. The proportion of children lost to follow-up was much higher in cohort II (25%, 368/1495) than in cohort I (9%, 25/287) ($P < 0.01$), but

Table. Baseline characteristics of the two study cohorts attending antenatal clinics in camps along the western border of Thailand, 1987–96

	Cohort I 1987–90[a] ($n = 287$)	Cohort II 1993–96[b] ($n = 1495$)	P
Mean (SD) maternal age (years)	26.6 (6.4)	25.4 (6.1)	<0.01
Mean (SD) gravida	3.8 (2.7)	3.5 (2.5)	0.07
No. (%) of primigravidae	71 (25)	382 (25)	0.83
Maternal malaria	63/287 (22%)	555/1495 (37%)	<0.01
Maternal anaemia at delivery	56/283 (20%)	353/1444 (24%)	0.11
Mean (SD) birthweight (g)			
All gravidae	2919 (457)	2872 (490)	0.14
Primigravidae	2700 (435)	2686 (468)	0.81
Multigravidae	2990 (468)	2937 (481)	0.14
Distribution of birthweight			
< 2000 g	7/283 (3%)	57/1346 (4%)	
2000–2499 g	34/283 (12%)	167/1346 (12%)	
2500–2999 g	117/283 (41%)	514/1346 (38%)	
⩾ 3000 g	125/283 (44%)	608/1346 (46%)	0.47

[a]Cohort I, before recognition of infantile beri-beri.
[b]Cohort II, after recognition of infantile beri-beri.

the reasons for withdrawal in cohort II were unrelated to the study. More than half of the mothers and their babies (58%, 212/368) left during periods of insecurity when armed groups attacked the camps. Overall, 86% (1292/1495) of the children in cohort II were followed for at least 6 months, the period during which most infant deaths occurred (88% in both cohorts).

Between 1987–90 and 1993–96 infant mortality rates declined from 183 (48/262) in cohort I to 78 (88/1127) in cohort II per 1000 live births. While the neonatal mortality remained stable [35 (10/287) and 33 (49/1467) per 1000, respectively], the risk of dying during the post-neonatal period fell by 79% (95% CI 65–87%) from 151 (38/252) to 36 (39/1078) per 1000 children alive at 1 month of age. The post-neonatal mortality (deaths between 1 month and 1 year of life) declined steadily during the 10-year period (Fig. 1). A more detailed analysis showed that in cohort I the risk of dying at 1–5 months of age remained as high as that in the neonatal period. This unusual temporal pattern of infant mortality had disappeared in cohort II (Fig. 2). The excess mortality seen in cohort I was related mainly to deaths of infants born with a normal birthweight. The risk of dying in infancy was reduced by 75% (95% CI 60–84%) between 1987–90 (cohort I)

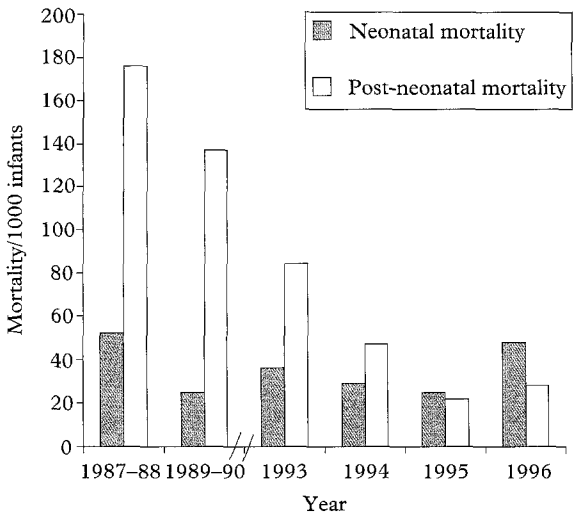

Fig. 1. Temporal pattern of neonatal (0–1 month) and post-neonatal (1–11 months) mortality in Karen infants living on the western border of Thailand 1987–96.

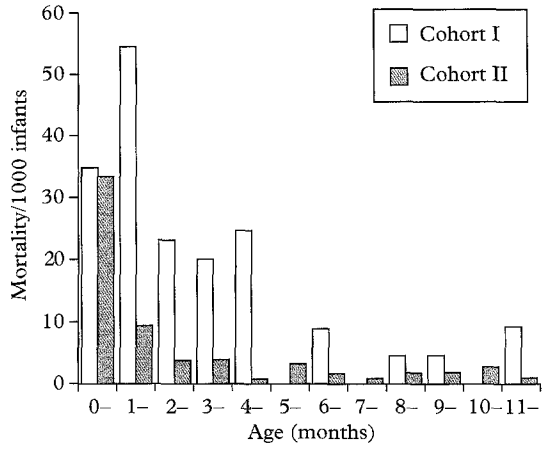

Fig. 2. Age-specific mortality rates from birth to 12 months of age in 2 study cohorts living on the western border of Thailand, 1987–96. Cohort I, before recognition of infantile beri-beri; Cohort II, after recognition of infantile beri-beri.

and 1993–96 (cohort II) in children who weighed more than 2500 g at birth (from 169 to 43 per 1000), whereas infant mortality rates were similarly high in the 2 cohorts of low birthweight infants, i.e. < 2500 g at birth (250 and 223 per 1000; relative risk = 0.9, 95% CI 0.5–1.7).

Thiamine deficiency was considered responsible for 40% (19/48) of all infant deaths in cohort I and 7% (6/88) in cohort II, giving a specific mortality rate of 73 (19/262, 95% CI 46–109) and 5 (6/1127, 95% CI 2–11) per 1000, respectively. As morbid events were not reported actively in cohort I, it is not known if some children presented with infantile beri-beri and survived, but this is considered unlikely. In cohort II, 84 infants presented with this syndrome (sudden respiratory distress, apyrexia, normal auscultation of lungs, enlarged liver, and rapid recovery after parenteral injection of thiamine or death within hours in case of profound shock on arrival), giving an overall incidence of infantile beri-beri of 75 (95% CI 60–91) per 1000. The majority (93%, 78/84) of these infants were treated successfully. During the same periods, mortality from acute respiratory infections did not change [15 (4/262) per 1000 in cohort I and 11 (12/1127) per 1000 in cohort II].

Discussion

Beri-beri was known in China as long ago as 2600 BC. The relationship to diet of this syndrome was

recognized through the pioneering work of Admiral Takaki of the Japanese navy between 1882 and 1887 (Takaki, 1906). In 1888, Hirota in Tokyo described sudden death in infants fed by mothers with beri-beri (Hirota, 1888). He called this 'infantile beri-beri', almost 40 years before the missing essential nutrient, the vitamin B_1 (thiamine) was first purified by Jansen & Donath (1926) working in the Eijkman Institute in Jakarta, Indonesia. Since that time thiamine deficiency has been recognized as a cause of peripheral, central, and autonomic nervous system dysfunction (dry beri-beri), cardiomyopathy with congestive cardiac failure (wet beri-beri), and severe lactic acidosis (Platt, 1967; Attas *et al.*, 1978; Campbell, 1984). Thiamine deficiency has also been implicated in the sudden unexplained nocturnal death syndrome (SUNDS, SIDS) which is common in East Asia (Lonsdale, 1990; Wong *et al.*, 1992; Munger *et al.*, 1996) although the evidence for this is less convincing. Before thiamine treatment became widely available approximately 5% of all adult beri-beri was of the fulminant or 'Shoshin' type. This had an 80–90% mortality rate within 12 h of admission. However with thiamine treatment the mortality fell to 20%. Although myocardial failure and lactic acidosis are thought to be primarily responsible for death in acute beri-beri, some authors have considered that central nervous system dysfunction resulting in acute respiratory failure may also contribute (Platt, 1967). The classical descriptions of beri-beri linked the disease to the change from crudely milled or unmilled (brown) rice to polished (white) rice (Plagnol & Dutrenit, 1956; Platt, 1967). The rice grain husk contains thiamine, and this is lost in the process of polishing.

In this population of displaced persons on the western border of Thailand the traditional practice of hill-rice cultivation, which would have resulted in crudely milled rice after harvesting, was replaced by supplies of polished rice, purchased in bulk and provided to feed the displaced population. Well-polished white rice is widely regarded by the population as being of higher quality than crudely milled or unpolished rice. In addition thiaminases are present in the fermented fish that is the staple rice flavouring, and also in betel nut and tea leaves, which are widely chewed. These factors may all have contributed to thiamine deficiency in the Karen population (Vimokesant *et al.*, 1975).

The pathogenesis of infantile beri-beri is undoubtedly thiamine deficiency, although other factors in the milk of lactating mothers with B_1 hypovitaminosis have also been implicated (Fehily, 1944). The infant is chronically depleted in thiamine because the mother is depleted. Intercurrent infections compound the problem by increasing demand for thiamine. We do not have biochemical confirmation of thiamine deficiency in the infants in this series, but the characteristic clinical presentation, occurring at around 2–3 months of age, and the rapid life-saving effect of i.m. thiamine, with full recovery from shock within hours, make it very likely that infantile beri-beri resulting from vitamin B_1 deficiency was the cause of this syndrome. This typical clinical presentation has been well described previously in Asia, although there are few recent reports (Fehily, 1944; Plagnol & Dutrenit, 1956; Thanangkul & Whitaker, 1966; Platt, 1967). Nutrition surveys in this Karen population have shown that the diet is relatively thiamine-deficient, especially during pregnancy and lactation even after introduction of antenatal thiamine supplementation. More recently, biochemical evidence of thiamine deficiency has been shown to be very common in lactating Karen women. Thiamine status was assessed during a prospective study from 30 weeks of gestation to 3 months post-partum. At delivery, 22% (8/36) of the women were thiamine-deficient (defined as an erythrocyte transketolase activity [ETKA] $\geqslant$ 1.20%). At 3 months post-partum 58% (15/26) of the women had thiamine deficiency (McGready *et al.*, 2001). After recognition of this lethal but readily treatable syndrome in infancy the peak in infant deaths at 1–5 months of age has gone, and post-neonatal infant mortality has fallen by 79%, mainly because of a reduction in deaths of infants weighing more than 2500 g at birth. In this refugee population infantile beri-beri was the single biggest killer in infancy, causing the death of 7% of all children. Infantile beri-beri is a readily preventable disease that nearly disappeared during the first half of the twentieth century. In the Philippines, infantile mortality from this disease decreased from 94 to 19 per 1000 between 1914 and 1930. In Thailand, this condition is extremely rare in well-fed urban populations, but in adjacent Laos it is still an important cause of infant death (D. Soukaloun, personal communication). Infantile beri-beri may be an important cause of infant mortality in rural areas in this region, and in special situations such as population movements, where polished rice is provided by relief agencies, it may be much more common than hitherto recognized.

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