A diagnosis and treatment gap for thiamine deficiency disorders in sub-Saharan Africa?

Bola Adamolekun and Laurent Hiffler

Department of Neurology, University of Tennessee Health Science Center, Memphis, Tennessee

Address for correspondence: Dr. Bola Adamolekun, M.D., FWACP, Department of Neurology, University of Tennessee Health Science Center, Memphis, TN 38163. badamole@uthsc.edu

Staple diets that are deficient in thiamine can result in low body thiamine levels, which may be subclinical or may manifest as a thiamine-deficiency syndrome. In many communities in the developing countries of Africa, the staple diets of polished rice or processed cassava are deficient in thiamine, and thus the communities are at high risk for marginal or frank thiamine deficiency unless their diets are supplemented by other sources of thiamine, such as protein meals and vegetables. African communities with large numbers of individuals in low socioeconomic strata are more likely to subsist on a monotonous diet of rice or cassava with minimal or no protein supplementation and are therefore particularly at risk of thiamine-deficiency disorders. Indeed, there is evidence of widespread biochemical thiamine deficiency from community-based studies in Africa. The protean manifestations of thiamine deficiency disorders in the developing countries of Africa are presented in this paper. We present evidence supporting the contention that there is a diagnosis and treatment gap for thiamine-deficiency disorders in Africa. We discuss research and clinical options for bridging the putative diagnosis and treatment gap for thiamine-deficiency disorders in the developing countries of Africa.

Keywords: thiamine; deficiency; beriberi, infant mortality; Africa

Introduction

The human body requirement for thiamine is exclusively dependent on regular dietary intake, as there is no significant mechanism for endogenous production of thiamine or for prolonged storage of thiamine in the human body. It is estimated that the body can store thiamine for 2–3 weeks. Staple diets that are deficient in thiamine would result in low body thiamine levels, which may be subclinical or may manifest as a thiamine-deficiency syndrome.

Thiamine deficiency is classically associated with diets consisting mainly of milled white cereals, particularly polished rice and highly refined wheat flour. Milling significantly reduces the thiamine content of cereals: the thiamine content of highly milled white rice is 0.08 mg/100 g compared with 0.33 mg in unmilled brown rice. Rice washing and cooking methods may result in additional losses of up to 45–60% of thiamine.1 Rice is the most important food source in the tropics. Over the last 50 years, West and Central Africa have seen a sixfold increase in the consumption of rice and have drastically reduced the consumption of traditional cereals, like sorghum and millet. This change in diet has increased the risk for thiamine deficiency, especially in communities where polished rice is preferred.

Cassava is the staple food of almost a billion people in the tropics and is a staple in most African communities. The processing of cassava to remove potentially toxic cyanogenic glycosides involves peeling, soaking, grating, pounding, and boiling. These methods are effective in eliminating much of the hydrogen cyanide in cassava, but also result in the elimination of all thiamine in cassava. The thiamine content of processed cassava meal is 0.00 mg/100 mL.1

In the developing countries of Africa, communities relying mainly on staple diets of polished rice or processed cassava are therefore at risk of marginal or frank thiamine deficiency unless their...
diets are supplemented by other sources of thiamine, such as protein meals and vegetables. Communities with large numbers of individuals in lower socioeconomic strata are more likely to subsist on a monotonous diet of rice or cassava with minimal or no protein supplementation and are therefore particularly at risk of thiamine-deficiency disorders. We present the protean manifestations of thiamine deficiency in the developing countries of Africa and contend that there is a diagnosis and treatment gap for thiamine deficiency disorders in Africa.

**Infantile thiamine-deficiency disorders**

Infantile beriberi is an acute thiamine-deficiency state mainly affecting infants breastfed by thiamine-deficient mothers. The content of thiamine in breast milk is related to the mother’s thiamine status. Infantile beriberi may present as cardiac or wet beriberi, neurologic or dry beriberi, or as the aphanic form of beriberi. Some clinical manifestations of infantile beriberi can mimic other disorders. Conversely, a significant proportion of infants admitted with other diseases may have thiamine deficiency complicating their illnesses. Infectious diseases like malaria or typhoid can precipitate beriberi: an increase in body temperature by 1°C may increase the basal metabolic rate by 10%, leading to increased utilization of thiamine. Similarly, critical illnesses may be associated with increased utilization of body thiamine, which may precipitate acute thiamine deficiency if the patient was marginally thiamine deficient.

**Infantile thiamine deficiency and infant mortality**

Conventional testing of thiamine deficiency using assays of thiamine-dependent erythrocyte transketolase is either unavailable or impractical in the rural hospitals in the developing countries of Africa where potential cases may be present. A high index of clinical suspicion is therefore required of the treating physicians if the diagnosis of infantile thiamine deficiency is not to be missed. This is particularly important because of the high mortality rate associated with the diagnosis of infantile beriberi. Indeed, unusually high infant mortality rates in infants with congestive heart failure may be prescient for a potential diagnosis of thiamine deficiency. A high infant mortality rate for infants with congestive heart failure at a hospital in Laos led to the recognition and treatment of infantile beriberi, with significant decline in hospital death rate. Persistence of a high infant mortality rate after the neonatal period with a second mortality peak before 6 months of age has been used as an epidemiological sentinel for the presence of infantile thiamine deficiency in a community. Recognition of infantile beriberi is particularly urgent because of the high rate of mortality and the potential for rapid clinical response to thiamine.

**Disparities in the rates of diagnosis of infantile beriberi between Southeast Asia and sub-Saharan Africa**

In several Southeast Asian countries, retrospective surveys of infants with a discharge diagnosis of thiamine deficiency have been conducted, presumably because the hospital systems and medical personnel in these countries are sensitized to diagnose and treat infantile thiamine deficiency. Infantile thiamine deficiency is well recognized as a persistent cause of infant morbidity and mortality in the developing countries of Southeast Asia. Recent studies have indicated a significant but clinically unapparent burden of thiamine deficiency in sick infants admitted to hospital in Laos, with a mortality rate of about 6%. Another study from Laos showed excess infant mortality in areas of thiamine deficiency compared with the national average. Identified multifactorial risk factors included the consumption of polished rice and thiaminase-containing fermented fish paste; the consumption of antithiamine compounds, such as betel nuts or tea, and postpartum food-avoidance cultural practices.

There is a high risk for thiamine deficiency in the developing countries of sub-Saharan Africa because of the staple monotonous diet of cassava with minimal protein supplementation in the impoverished rural communities. One study from Ghana confirmed evidence of a widespread biochemical thiamine deficiency in children aged 6 months–6 years. Additionally, some sub-Saharan countries suffer from very labile food security, which further increases the risk. In this regard, populations in refugee or internally displaced camps are at risk of thiamine deficiency. In 2001, Médecins Sans Frontières witnessed many cases of thiamine deficiency in Angola during a nutritional crisis. In 2004, the French authorities declared an epidemic of infantile beriberi in the Mayotte. A systematic review of the literature, however, failed to reveal clinical case series or reports of...
diagnosed cases of thiamine deficiency disorders in infants and children in sub-Saharan Africa, even in the populations most likely to be at risk. For example, published papers indicated that lower respiratory infections and severe anemia due to malnutrition and malaria were the most common causes of cardiac failure in African infants and children.\textsuperscript{9–11} Mortality rates were as high as 24%.\textsuperscript{12} In one study, 91% of children with cardiac failure had parents in low socioeconomic strata.\textsuperscript{11} However, none of the papers mentioned or discussed thiamine deficiency as a probable or possible cause of cardiac failure or mortality in their patients. The potential contribution of thiamine deficiency disorders to the high infant mortality rates in these patients is therefore unknown.

There is a strong concern that there is a large disparity in the rates of diagnosis and treatment of infantile thiamine deficiency in sub-Saharan Africa when compared with the developing countries of Southeast Asia. This is potentially ominous, because sub-Saharan countries constitute 14 of the 15 countries with the highest infant mortality rates, and it is unknown to which extent untreated infantile thiamine deficiency contributes to the high infant mortality rates in these countries.

**Thiamine deficiency disorders in children and adults**

**Confirmed thiamine deficiency disorders**

Epidemics of beriberi manifesting with sensory neuropathy and gait ataxia have been described in children and adults within segments of the African population subsisting on diets that provide marginal or submarginal intakes of thiamine in prison populations\textsuperscript{14,15} and in garrisoned troops.\textsuperscript{16} Seasonal ataxic syndrome is an acute thiamine-deficiency state that has occurred in epidemics in parts of Western Nigeria during the rainy season and manifested with clinical features of Wernicke’s encephalopathy. Studies have confirmed that seasonal ataxic syndrome is a thiamine-deficiency disorder that occurs in low-income individuals with marginal thiamine deficiency. An acute thiamine deficiency state is precipitated in these individuals by the consumption of African silkworm (\textit{Anaphe venata}) larvae, which is widely available during the rainy season.\textsuperscript{17} Studies have confirmed the presence of heat-stable thiaminases in the larvae.\textsuperscript{18} Tropical ataxic neuropathy (TAN) is a syndrome of sensory polyneuropathy, sensory ataxia, bilateral optic atrophy, and bilateral sensorineural deafness described in several African countries. The cardinal clinical features of TAN are similar to those of thiamine deficiency.\textsuperscript{19} A therapeutic trial of thiamine in these patients has indicated that it is a thiamine-deficiency state.\textsuperscript{20}

**Probable thiamine deficiency disorders**

There are some neurologic syndromes of undetermined etiology occurring in parts of Africa that are probable thiamine-deficiency syndromes but have not been conclusively investigated and confirmed to be due to thiamine deficiency. One of these is epidemic spastic paraparesis (konzo), a severely debilitating disorder characterized by abrupt onset of paraplegia occurring in patients subsisting almost exclusively on a diet of improperly processed cassava roots.\textsuperscript{21} Epidemics have been reported from several countries in Central and East Africa affecting hundreds of thousands of people, predominantly children and young women. The etiology remains unknown, but several aspects of the clinical presentation are suggestive of a thiamine-deficiency disorder.\textsuperscript{19} Thiamine levels have never been tested in these patients, and a therapeutic trial of thiamine has never been performed.

Another probable thiamine-deficiency disorder is the epidemic optic neuropathy associated with peripheral neuropathy, which has been reported in Tanzania and Somalia.\textsuperscript{22,23} The clinical description of the syndrome is quite similar to the epidemic of optic and peripheral neuropathy described in Cuba, where patients were found to be thiamine deficient and responded to vitamin B supplementation.\textsuperscript{24} The epidemic optic neuropathy syndrome may well be a \textit{forme fruste} of TAN, which also presents with optic neuropathy and peripheral neuropathy. Although acute cases of epidemic optic neuropathy have been successfully treated with vitamin B supplementation in Tanzania,\textsuperscript{22} thiamine levels have never been tested in these patients, and a therapeutic trial of thiamine has never been conducted.

**Bridging the diagnosis gap for thiamine-deficiency disorders in Africa**

In several Southeast Asian countries, hospitals have a low threshold for the diagnosis and treatment of infantile thiamine deficiency, and retrospective or
prospective data can be readily collected on patients with a discharge diagnosis of thiamine deficiency. In that scenario, retrospective studies will be suitable and cost-effective.

In the sub-Saharan African countries, there does not seem to be any evidence for a similar low threshold for the diagnosis or treatment of infantile thiamine deficiency. There are few reports in the literature of diagnosis or treatment of infant thiamine deficiency, and the contribution, if any, of thiamine deficiency to the high infant mortality rates in these countries is unknown.

Studies providing objective and demonstrable evidence of the possible contribution of infantile thiamine deficiency to the high infant mortality rates in these communities will be needed to galvanize sub-Saharan African countries to develop aggressive measures for the diagnosis and treatment of infantile thiamine deficiency.

**Prospective or retrospective studies?**

In the absence of a low threshold for diagnosis, retrospective studies, such as verbal autopsies, are not likely to be useful as an estimate of infant mortality from thiamine deficiency. Prospective studies would be the preferable option in those countries.

Prospective studies could be planned in some countries as part of a demonstration research project. Thiamine levels can be measured in breastfeeding mothers, apparently healthy infants, severely malnourished children, hospitalized infants, and infants with congestive heart failure to determine prevalence of thiamine deficiency in these subgroups. Using a case–control methodology, objective thiamine status can be correlated with socioeconomic status, diet, and selected blood chemistry parameters to evaluate their utility as surrogates of thiamine deficiency.

Sentinel surveillance studies may be required to provide rapid diagnostic and therapeutic response to cases of konzo and epidemic optic neuropathy wherever they may occur.

Development of point-of-care rapid testing not requiring advanced laboratories is essential in order to be able to scale up the number of these studies and to get reliable data from areas where thiamine deficiency is poorly documented.

**Evaluation of long-term sequelae**

Apart from causing infant mortality, thiamine deficiency may have unappreciated long-term consequences on neurological development. Thiamine deficiency is a possible cause of delayed visual maturation in Karen refugee infants. Infantile thiamine deficiency has been associated with delayed language development and epilepsy in Israeli children. A study in the Democratic Republic of Congo (DRC) demonstrated a pervasive subclinical neurocognitive abnormality in children from low socioeconomic classes subsisting on high-cassava diet. Cohorts of patients with thiamine-deficiency disorders can be followed over time and evaluated for possible short-and long-term sequelae of thiamine deficiency with serial neuropsychological testing, such as with the Kaufman assessment battery for children and the Bruininks–Oseretsky test of motor proficiency used in the DRC study.

**Conclusions**

There is a need for prospective epidemiological and clinical studies in selected sub-Saharan African countries that can demonstrate the putative contribution of infantile thiamine deficiency to the high infant mortality rates in these countries. This may provide the impetus for fashioning national policies on the treatment and prevention of thiamine-deficiency disorders.

Erythrocyte transketolase activity—while being a gold standard for the accurate evaluation of the thiamine status of the body—is not usually available in resource-poor settings and cannot allow immediate diagnosis of thiamine deficiency in life-threatening situations. In the absence of specific diagnostic tests, a therapeutic thiamine challenge is the only way to diagnose thiamine-deficiency disorders, as rapid clinical improvement is usually seen with acute thiamine deficiency.

There is an urgent need to sensitize health care workers in the developing countries of Africa to develop a high level of clinical suspicion for thiamine deficiency and a low threshold for administration of thiamine, particularly when infantile thiamine deficiency is suspected. There is also a need for sentinel surveillance programs for rapid intervention, including diagnostic testing and thiamine therapeutic challenge, in future epidemics of probable thiamine deficiency disorders, such as konzo and epidemic optic neuropathy.

**Competing interests**

The authors declare no competing interests.
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