Rickets, BeriBeri, and Iron Deficiency: micronutrient deficiencies in children

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ABSTRACT

Some "forgotten" micronutrient deficiencies continue to be common in children. Deficiencies of vitamin D and/or calcium can cause rickets, a crippling condition related to poor mineralization of growing bones. Rickets is diagnosed by identifying skeletal deformities, elevation of alkaline phosphatase levels, and abnormal epiphyses on x-ray. Treatment is with vitamin D and calcium. Prevention hinges on improving the daily intake of calcium, regular sun exposure, or dietary supplementation. Beriberi is due to thiamine deficiency. Infants with beriberi present in heart failure while older children present with neurological abnormalities. Treatment is with thiamine, and prevention requires alterations to improve dietary thiamine intake – by supplementing mothers of breastfed babies, increasing legume and unpolished rice intake, and diversifying diets. Iron deficiency continues to be a problem for nearly half of the world's children. Bhutan has made strides to eliminate this problem through active de-worming programs and iron supplementation programs.

Keywords: Anemia; Beriberi; Calcium; Iron; Nutrition; Rickets; Thiamine; Vitamin D.

INTRODUCTION

Recent scientific advances are leading to improved pediatric nutrition. Nonetheless, calcium and vitamin D deficiencies are increasingly recognized in many areas, and thiamine deficiency is reported particularly in Asia. Iron deficiency is widespread throughout the world. Here, we review: 1) Rickets due to calcium and vitamin D deficiency, 2) Beriberi due to thiamine deficiency, and, 3) Iron deficiency.

RICKETS

Definition and History

Rickets is a condition of bony deformity related to poor mineralization of growing bones. While it was initially associated with crowded living conditions in northern latitudes[1], Vitamin D deficiency was established as the primary cause of rickets quite some time ago. More recently, however, rickets has "re- emerged" in sunny regions where children receive inadequate quantities of dietary calcium[1-6]. However the prevalence of rickets in Bhutan is unknown.

Physiology and Pathophysiology

Growing bones depend on calcium and vitamin D. Vitamin D, whether from oral intake or sunshine - supported synthesis in the skin, is hydroxylated in the liver to form 25-hydroxyvitamin D, the form of vitamin D which serves as the basis of the biochemical testfor deficiency. A second hydroxylation, in the kidneys, forms 1,25-dihydroxyvitamin D. In the intestines, 1,25-dihydroxyvitamin D increases the absorption of calcium.

With inadequate sun exposure and insufficient oral vitamin D, intestinal absorption of dietary calcium decreases, and serum calcium levels fall. Consequently, parathyroid hormone levels rise, and calcium is released from bones[7-8]. This process leaves insufficient bone calcium for mineralization. Longitudinal growth is impaired, growth plates widen, and weakened bones bend.

Presentation and Risk Factors

Clinically, rickets presents as bony deformities – often with the legs bowed out (genu varus) or turned in (knock-knees, genu valgum) (Figure 1), with widened wrists and ankles, and with "beading" or "pearling" of the ribs[9]. Less common findings include anterior bowing of the lower legs (sabre tibia), lateral indentation of the chest (Harrison's sulcus), and hypoplasia of dental enamel. Low circulating calcium levels can trigger tetany. After bone growth is completed, vitamin D deficiency can lead to osteomalacia without deformed bones.

Rickets due to vitamin D deficiency presents during the first year of life with hypocalcemia and early bony changes, or in the second year of life with delayed walking and limb deformities. However, many rachitic children are asymptomatic[7].

Figure 1. Bangladeshi Children with Rachitic Leg Deformities

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Fifty years ago, a later presentation of rickets was identified when vitamin D-replete South African children with dietary insufficiency of calcium presented after the first year of life without hypocalcemia but with marked leg deformities[10].

More recently, calcium-deficient rachitic children were identified in Nigeria[2] and Bangladesh[4] [and beyond[1]][5]. Most rickets relates to vitamin D deficiency in China and to calcium deficiency in India. Rickets occurs in Bhutan, but the causes and prevalence are unknown. Several correctable risk factors have been identified[11-13]. Supplementation with vitamin D and/or calcium, depending on which problem is most prevalent locally, can prevent rickets[14-16].

Diagnosis

The diagnosis of rickets requires careful attention to clinical findings. Blood levels of 25-hydroxyvitamin D are low in children with vitamin D deficiency, and calcium levels are mildly low to normal with rickets of either cause. Alkaline phosphatase levels are markedly elevated. Radiographs show cupping, widening, and fraying of growth plates, especially at the wrists and knees[17] in Figure 2.

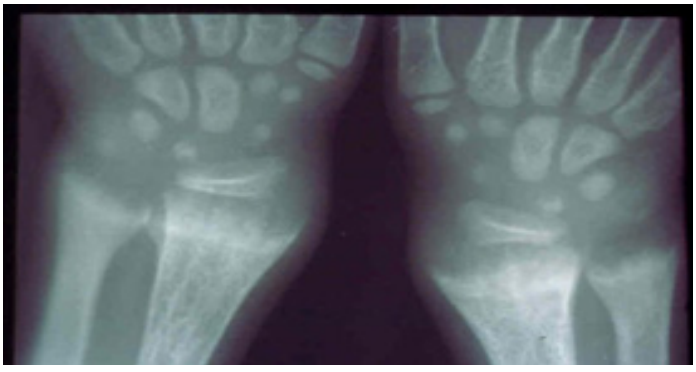

Figure 2. Typical Wrist X-Rays of Rachitic Child demonstrating wide, frayed, cupped epiphyses

Treatment

Vitamin D can be given orally or intramuscularly. Doses range from an average of 1000 IU orally daily to 300,000 IU every three months intramuscularly. Calcium should be provided orally -1000 mg of elemental calcium daily (in addition to whatever the child regularly consumes). Treatment usually continues for six months. Concurrently, lifestyle changes should be implemented to ensure that adequate sun exposure (or vitamin D supplementation) and calcium intake continue[18].

Clinicians should also be alert to the possibility of genetic variations of rickets[19,20] and to rickets secondary to renal disease. With treatment and ongoing lifestyle changes[21] children with rickets should be able to recover well.

BERIBERI

Definition and History

Beriberi results from thiamine (vitamin B1) deficiency. Wet beriberi involves infantile cardiac failure. Dry beriberi involves neurologic dysfunction in older children and adults[7]. Beriberi is again being seen in some parts of the world[22]. Thiamine deficiency has been suspected in school-based outbreaks of peripheral neuropathy in Bhutan, and thiamine deficiency increases as the school year progresses[23].

Physiology and Pathophysiology

Thiamine is found in meats, legumes, vegetables and grains most specifically in the husk or bran covering the grain. However, when rice or other grains are "polished" by thorough milling, the thiamine- rich husk is removed. Thiamine deficiency is most common in breastfeeding infants whose mothers are thiamine-deficient and in children who eat a diet depleted of thiamine. Some teas and betel nuts also contain or can be contaminated with thiaminases that adversely affect the absorption and utilization of thiamine. Recently, childhood beriberi has been reported in Bhutan[23], Brazil[24], Laos[25] and Cambodia[26].

Presentation and Risk Factors, Treatment

Wet beriberi presents during the first year of life with lethargy, poor feeding and respiratory distress due to heart failure. Erythrocyte transketolase assays were previously used as a proxy for thiamine activity but actual blood thiamine and thiamine diphosphate levels can now be measured. In areas where most infants are thiamine-deficient (thiamine diphosphate level less than 70 nmol/L), not all have symptoms[27] but heart failure is seen in those with the lowest levels (<30 nmol/L)[28]. Thiamine deficiency and heart failure correct within one to two days following intramuscular injection of 50mg of thiamine[29].

Critically ill children sometimes have low thiamine levels. This could be either from a pre-existing deficiency or from illness-induced changes[24,28].

Some Bhutanese school children were found with neurologic symptoms with beriberi, including mild paresthesias and even ataxia[23]. Oral treatment with 10mg of thiamine daily for one month is curative for children with non-life-threatening deficiencies.

Public Health Interventions

At a public health level, children living in areas of thiamine deficiency benefit from analysis of dietary factors. Where beriberi is common, community-wide changes in food preparation and diet are needed. Potential interventions include changing milling procedures, eating rice bran, diversifying diets to include foods high in thiamine, avoiding ingestion of products containing thiaminases, fortifying institutional foods, and giving thiamine supplements. Supplementation of breast-feeding mothers can help infants[30].

IRON DEFICIENCY

Definitions and Epidemiology

Iron deficiency is the world's most common nutritional problem. Approximately 43% of all pre- school-aged children in the world and 25% of school- aged children are anemic[31], and iron deficiency accounts for half of that anemia. Iron deficiency is also a problem

for non-anemic children; 42% of the world's young children are iron deficient[31]. Children in South America, middle Africa, and the Indian subcontinent are most severely affected[32]. In Bhutan, 43.8% of children six to 59 months of age were anemic in 2015[33].

Hemoglobin levels vary with age[7,34]. At sea-level, a hemoglobin concentration of less than 10 gm/dl is indicative of anemia in a child four to six months old. A hemoglobin level should be at least 10.5 gm/dl by 9 months of age, 11 gm/dl for older pre-schoolers, 11.5 gm/dl for 5-11 year olds, and 12 for adolescents. Children living at high altitude have increased hemoglobin concentrations.

Risk Factor-Based Public Health Interventions

Common sources of iron are meats and dark green leafy vegetables. In populations with a high prevalence of anemia, each 1g/dl increase in hemoglobin concentration results in a 24% reduction in all-cause mortality[31]. Improved dietary intake of iron-rich foods would help reduce anemia, but other modifiable factors are also relevant.

Table. Food Sources of Relevant Micronutrients

Micronutrient	Foods with high to moderate amounts of micronutrient	Foods affecting absorption	Tips for eating
Calcium	Milk and milk products: -Milk -Curd -Yogurt -Cheese -Canned sardines -Sesame seeds -Almonds and other nuts -Tofu and other soya products -Bok choy -Kale -Turnip greens -Other green, leafy vegetables - Broccoli -Legumes and pulses	-Oxalic acid (found in spinach, rhubarb and some beans) inhibits absorption of calcium	-Eat a variety of green, leafy plants and vegetables since some contain high amounts of calcium, and others contain oxalic acid
Vitamin D	*Vitamin D is made in the skin when skin is exposed to sunlight* -Eggs -Fatty fish -Mushrooms -Meat		
Thiamine	-Pork -Legumes and pulses *(peas, navy beans, black beans, lentils, soybeans, Bengal gram/chickpeas, winged beans, etc.)* -*Whole grains (thiamine is found in the outer layer of grain. Polished and milling removes the bran layer that contains thiamine)* -Rice bran -Buckwheat -Barley -Oatmeal -Wheat -Sunflower seeds -Nuts -Orange juice	-Thiaminases destroy thiamine: Thiaminases are found in -certain raw fish -betel nut -certain ferns	-Avoid exclusive use of polished white rice that is not enriched with thiamine -Do NOT RINSE enriched rice prior to cooking -Choose whole grain rice such as red rice or brown rice -Eat a variety of grains and legumes/pulses

Iron	Heme source of iron: -Meat -Chicken -Fish Non-heme source of iron: -Eggs -Beans (legumes/pulses) -Sunflower, sesame and pumpkin seeds -Nuts -Mushrooms -Spinach -Radish leaves -Cauliflower greens -Dark green leafy vegetables -Broccoli -Dried fruit (apricot, dates, raisins)	-Ascorbic acid (Vitamin C) enhances non-heme iron absorption, and counteracts absorption inhibitors such as tannins and phytates (Some foods high in vitamin C are tomatoes, chili peppers, lemons, oranges and other citrus) -Animal source protein enhances non-heme iron absorption -Tannins (tea) inhibits iron absorption -Phytates (found in beans and legumes) inhibit absorption -Calcium inhibits absorption	-Eat non-heme iron sources with foods high in vitamin C such as tomatoes and chili peppers -Avoid excess tea -Some processed foods such as cereals, bread, flour and pasta may be enriched with iron

Adapted from:
U.S. Department of Agriculture, Agricultural Research Service. 2014. USDA National Nutrient Database for Standard Reference, Release . Nutrient Data Laboratory Home Page, http://www.ars.usda.gov/nutrientdata

Dietary reference intakes : the essential guide to nutrient requirements / Jennifer J. Otten, Jennifer PitziHellwig, Linda D. Meyers, editors http://www.nal.usda.gov/fnic/DRI/Essential_Guide/DRIEssentialGuideNutReq.pdf

Transplacentally-acquired iron is usually sufficient for the first six months of life. However, an iron-deficient mother may not supply adequate iron stores in utero or in her breast milk. Pregnant and lactating women should eat a diet rich in iron.

Delaying cord clamping for 30-180 seconds is effective in increasing hemoglobin and ferritin levels[35]. Delayed cord-clamping has been the accepted standard of care in Bhutan since 2013, and health care professionals elsewhere are now following suit. However, increasing red cell volumes in newborns also gives an increased risk of jaundice.

Cow milk ingestion in the first year of life is associated with milk protein intolerance and microscopic gastrointestinal blood loss in about 30% of babies. Also, cow milk iron is poorly bioavailable for human babies. Infant use of cow milk is associated with iron deficiency by stimulating blood loss, providing inadequate iron intake, and displacing intake of other foods[36,37]. Babies should breastfeed (or be provided with infant-specific formula) for the first year of life.

Helminth infections cause gastrointestinal blood loss. In areas where hookworm infection is common, episodic presumptive treatment with albendazole is associated with improved hemoglobin concentrations[38]. Regular de-worming is common in Bhutan

Diagnosis

The clinical presentation is non-specific, varying from asymptomatic to fatigue to congestive heart failure. In an anemic child with an otherwise negative history for hemolysis and chronic illness, a therapeutic trial of iron would be an acceptable diagnostic test. Giving 3-5 mg/kg/day of elemental iron for two months leads to an elevation in hemoglobin concentration if iron deficiency is the cause of anemia.

A low reticulocyte count in the face of anemia implies that the anemia is hypoproductive. Hypochromic microcytic cells on a blood smear (or low mean corpuscular hemoglobin concentration and low mean corpuscular volume) are highly suggestive of iron deficiency. Low iron binding saturation strongly supports a diagnosis of iron deficiency. The most useful blood test is the ferritin level, which reflects the degree of iron stores; however, the ferritin level can be falsely elevated in children with inflammatory conditions.

Treatment

First, elemental iron should be provided in a dose of 3-5 mg/kg/day for at least several months. Second, it is important that potential causes of iron deficiency are also treated – whether dietary inadequacy, helminth infestation, or chronic blood loss.

In populations where iron deficiency is common, widespread supplementation can be associated with a 49% reduction in anemia, a 76% reduction in iron deficiency, and improved cognition[39-41]. When more than 20% of children in an area are anemic, it is suggested that they receive a single weekly dose of oral elemental iron; 25 mg for preschoolers and 45 mg for school-aged children[40]. Wisely, Bhutanese schools adopted an "Iron Day" program for weekly iron supplementation for school children[42].

CONCLUSIONS

Nutritional deficiencies are common; previously "forgotten" conditions like rickets and beriberi are increasingly identified, and iron deficiency continues to silently plague half the world's children. Promoting dietary enhancements by incorporating the foods mentioned in the Table can help. Awareness of regional situations is necessary for targeted public health measures and clinical interventions.

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