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PERSPECTIVE

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Importance of micronutrient supplementation in children with congenital heart defects in Nigeria

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Abstract*:* The prevalence of congenital heart defects is increasing globally. Improvements in surgical techniques have resulted in increased life expectancy for individuals with heart defects. In developing countries, it is not unusual to find children with simple congenital heart defects presenting with complications (nutritional and non-nutritional) due to delay in surgical correction.
Data on nutritional deficiencies in children with heart diseases are rare, more so, those on micronutrient deficiencies. Macro- and micronutrient deficiencies are common among children with un-operated congenital heart defects, especially in those on chronic diuretic therapy. It is pertinent that the need for studies on the prevalence of micronutrient deficiencies and effects of micronutrient supplementation in these children be emphasized.
Therefore, the objective of this paper is to highlight the importance of micronutrient supplementation in children with un-operated congenital heart defects in Nigeria.

Key words: micronutrients, malnutrition, children, congenital heart defects, Nigeria

Introduction

Untreated congenital heart defects (CHD) either cyanotic or acyanotic can impact severely on the ability of the patient to ingest or absorb nutrients sufficient to sustain well being and foster proper growth due to recurrent/chronic heart failure or hypoxia. The frequency of diagnosis of CHD is increasing.[1] The incidence has increased from about 48.4 per 10,000 live births in the 1980's to 146 per 10,000 live births in the recent past,[1]probably due to better diagnosis and management, thereby creating a significant population with need for proper, prompt and effective healthcare.

Half of the children with heart defects require at least one surgical operation[2] either in the immediate neonatal period or later in childhood to achieve optimal life expectancy. Improvement in surgical techniques has positively influenced the outcome of CHD. In the past, more than 50% of children with CHD died before their first birthday, where as 85% of children with CHD now survive into adulthood.[3] The increasing survival of children with CHD brings to the fore the need for nutritional management to ensure adequate growth and development. Adequate nutrition before surgery has been shown to have both immediate and long term effect on post-operative outcome especially in less privileged regions of the world with poorly equipped facilities for prompt and proper cardiac interventions. [4-6]
It is not unusual to find children with simple heart defects presenting late for surgery either due to inability of the cardiac centre to provide the immediate needed interventions or due to a delay in accessing funding for the procedure.[6] The delay in surgical correction of CHD places the individual at risk of nutritional deficiencies. Ratanachu-EK *et al*[7] showed that malnutrition occurs early in this group of children with about 40% of neonates being malnourished before surgery. In addition, Thommessen *et al*[8] reported a 50% prevalence of stunting amongst toddlers with CHD in a study involving 40 children. The prevalence of malnutrition is higher in children with poor access to healthcare such as may occur in developing countries. For instance, a hospital-based study from Lagos, south-west Nigeria involving 73 children with CHD reported protein energy malnutrition (PEM) in 90.4%, with 61.2% having severe form of malnutrition.[5] PEM seldom occurs in isolation, other macronutrient and micronutrient deficiencies often coexist with it. Information on micronutrient status in children with CHD is not readily available. It has however been documented that amongst the general paediatric population of Africa,[9] 24% have zinc deficiency, 20% have iron deficiency and 40% are iodine deficient.

Malnutrition has been implicated in two-thirds of childhood mortality globally and this has formed the basis for aggressive nutritional management in children with common childhood illnesses.[10] A review by Bhutta[11] on micronutrient needs of malnourished children found 11% of under-five mortality directly attributable to four

micronutrient deficiencies (vitamin A, zinc, iron and iodine). Despite the growing evidence of micronutrient deficiencies in children, nutritional management is still focused mainly on PEM, with little or no emphasis on micronutrients.

Nutrition and Congenital Heart Defects

There is a causal relationship between nutrition and CHD such that prenatal nutrition impacts on the structure of the developing heart, while postnatal nutrition mostly affects the functionality of the developed heart. Poor intake of micronutrients is widespread and may result from several factors including poor soil nutrient content. There is variable micronutrient soil content in Nigeria and other parts of Africa.[12,13] In particular, there are recorded areas with low soil micronutrients content within towns and villages located in south-south and north-central Nigeria.[12,14] A recent publication[15] from north central Nigeria has also revealed low selenium content of tubers grown in parts of Abuja, Niger, Benue and Kogi states. Consumers of such products are likely to develop selenium deficiency unless food is supplemented with micronutrients. Supplementation of food with selenium in Keshan province of China drastically reduced the incidence of Keshan disease, an endemic form of cardiomyopathy.[16] Although, Keshan disease have not been reported in Nigeria, 76.9% of women with peripartum cardiomyopathy in Kano had serum selenium levels below 70µg/L, thus suggesting the likely role of selenium deficiency in the aetiopathogenesis of peripartum cardiomyopathy. It is not clear if some of the cases of dilated cardiomyopathy in children in Nigeria are selenium related.

Beside selenium, zinc and copper contents of some Nigerian foods have been shown to be low, though with some regional variation.[17,18] A study involving children from the humid-forest zone of south-east Nigeria documented 59% of children, aged 2-5years, consuming zinc at levels below the dietary reference intake of 3-5mg/day.[18] This low intake is occurring in the background of high dietary phytate, fibers and lignin in the staple food. It is therefore not surprising that 20% of under-5 children in Nigeria suffer from zinc deficiency.[19] The figure is even higher in the moist savannah zone of the country with states in the north-central area having 36.5% of under-5 children with zinc deficiency.[19] Mean serum copper and zinc levels of 2.00-2.12µmol/l and 12.6-14.9µmol/l, respectively was documented in malnourished under-5 children in Jos, north-central Nigeria.[20] Other geopolitical regions have also documented micronutrient deficiencies. For instance, a study from south-west Nigeria reported selenium deficiency in 18.6% of healthy controls and 71.4% of HIV infected children.[21]

Children with CHD are at increased risk of micronutrient deficiencies because of their tendency to have chronic hypoxia and congestive heart failure necessitating the use of antifailure drugs that may impair appetite, induce anorexia, feeding intolerance and increase nutrient excretion.[22] Loop diuretics, for instance, have been shown to increase urinary excretion of micronutrients, including thiamine, calcium, selenium and zinc, while other medications such as angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and thiazides induce mainly zinciuria and hypozincemia.[23] In a recent study[24] involving 41 children with CHD in Benin, south-south Nigeria, serum zinc levels were lower in children on diuretics compared to those not on diuretics, with some of the children having zinc levels below 70µg/dl. Although zinc levels were comparable to those of children without CHD, the values were generally lower in children with CHD, thus confirming the added risk of nutritional deficiencies in children with CHD. This finding was corroborated by a study[25] from Egypt among 30 children with cyanotic congenital heart diseases that showed low levels of serum zinc and selenium in children with CHD as against their age-matched counterparts with normal hearts. In that study, it was suggested that low serum trace elements had important role in the pathogenesis of myocardial damage in congenital cyanotic heart diseases.[25]

Effects of micronutrient deficiencies on the heart

Mild micronutrient deficiency could exacerbate existing cardiac dysfunction while severe deficiency may cause heart failure or even cardiomyopathy. Of interest is that the cardiac abnormalities may develop even before the classical clinical features of the micronutrient deficiency manifest. Several hypotheses have been proposed to explain the mechanisms behind cardiac dysfunction in micronutrient deficiencies.

Antioxidant role: Patients with CHD are more susceptible to the effects of micronutrient deficiency because of increased oxidative stress associated with the condition. Zinc, copper and selenium are antioxidants and deficiency state could results in myocardial damage and cellular apoptosis.[26] The antioxidant role of zinc is mediated through zinc-dependent superoxide dismutase,[26,27] while that of copper is through copper-dependent superoxide dismutase.[26,27] Copper restriction in experimental animal studies was found to be associated with increased risk of myocardiocyte oxidative damage, myofibrillar disarray and mitochondrial fragmentation. Decreased Cytochrome C oxidase activity in copper deficiency could result to mitochondrial impairment and consequent cardiac dysfunction.[27] Selenium, on the other hand, is a constituent of the antioxidant enzyme glutathione peroxidase. Selenium deficiency has been associated with the endemic form of cardiomyopathy commonly found in regions with soil selenium deficiency in China.[27] Selenium-deficient cardiomyopathy in humans on long-term selenium-deficient total parenteral nutrition has also been described in Western countries.[26] Selenium deficiency leads to increased lipid peroxidation and, hence, increases in oxidative stress. Morphometric analysis of cardiac specimen from selenium-deficient rat revealed separation of cardiac microfibrils and Z-lines, mitochondrial ultrastructural changes such as fragmentation and loss of cristae, and increase in mitochondrial

volume density.[27] To corroborate the antioxidant role of micronutrients, a study in adults with acute coronary syndrome have documented a correlation between serum copper, zinc, iron and selenium levels with extent of myocardial damage.[28]

Role in cardiac cytoskeleton: Iron, zinc and copper are needed in collagen synthesis. Deficiency state has more profound effect in the fetus and early infancy. Neonates with zinc deficiency show higher rates of congenital valvular defects and increase in other congenital malformations.[26] In zinc-deficient rats, the activity of deoxythymidine kinase is reduced leading to decreased DNA, protein, and collagen synthesis.[26,28] This observation could explain the myocardial dysfunction and heart failure in humans with prolonged zinc deficiency.[29] Impaired collagen synthesis could alter the cytoskeletal structure of the heart causing increase in cardiac dimension, distortion of valvular apparatus and increased distensibility of blood vessels.[26,28] Defective structural components of vascular endothelium and myocardial tissues could occur even in mild copper deficiency. Animals with severe copper deficiency have died of vascular aneurysm and rupture of cardiac ventricle.[28] Lysyl oxidase, an enzyme required for cross-linkages in connective tissues, utilizes copper ions in the oxidative deamination of peptidyl lysyl groups in tropocollagen and tropoelastin.[16,26]

The peptidyl α-aminoadipic-δ-semialdehyde formed readily condenses with neighbouring aldehydes to form intra- and inter chain cross-links. This action is required for cohesion, stability and adequate functioning of connective tissues, absence of which may result in distortion of cardiovascular apparatus. It is not certain if the observations in animal studies occur in humans. However, in a study involving 30 elderly patients with chronic heart failure, high-dose multiple micronutrient supplementation for 9months yielded a 5.3% increase in the left ventricular ejection fraction with a concomitant decrease in left ventricular volume,[30] suggesting that micronutrient deficiencies may alter cardiac ventricular dimensions and left ventricular functions.

Protection against cytopathic viruses: Zinc is essential in cellular and humoral immune functions and its deficiency adversely affects handling of pathogenic viral organisms.[26,31] Zinc is a co-factor for thymulin, a thymus hormone, critically important for the maturation and functioning of T cells.[26] Zinc is involved in monocyte/ macrophage development and regulates its phagocytic and proinflammatory cytokine production.[26] Zinc deficiency affects the balance between the Th-1 and Th-2 cells,[26,32] thereby weakening T-cell mediated immune response.

In adult volunteers[33] given zinc deficient diet, serum thymulin activity and generation of T helper subset 1 cell cytokines were reduced within 2-3 months of institution of such diet even before plasma zinc concentration began to show significant decrease. These properties account for the overwhelming role of zinc in the control of acute respiratory infections and diarrhea diseases in children.

Selenium on the other hand, has stimulating effects on the immune system and its deficiency may result in defective immune function and increased susceptibility to pathogens. Publication by Gomez *et al*[31] as in 2001 on studies in mice revealed the increase susceptibility of the heart to coxsackie B1 and echovirus 9 viruses among rats fed on selenium deficient diet compared to the control group. Infection with viruses induces myocardial damage, poor contractility and eventual systolic dysfunction which with chronicity may result in dilated cardiomyopathy.

Detoxification of xenobiotics: Selenium interacts with cardiotoxic agents and protects the myocardium and blood vessels from their adverse effects. In a study by Tacyildiz *et al*[32] in children with anthracycline-induced cardiac toxicity, selenium supplementation for several months was shown to decrease Prohormone Brain Natriuretic Peptides levels and improve echocardiographic findings. Although the involvement of other micronutrients in detoxification has not been clearly documented, studies in the future may clarify their roles in cardioprotection.

Conclusions

Micronutrient deficiencies are prevalent and do contribute to the morbidity in children with CHD. Data on the magnitude of micronutrient deficiencies in children with congenital heart defects are rare in most developing countries including Nigeria. At the moment, micronutrient supplementation is not regarded as part of normal protocol in the management of children with congenital heart defects. Therefore, there is need to create awareness of the prevalence of nutritional deficiencies in children with CHD and probably instigate well-structured studies to document the magnitude of micronutrient deficiencies in children with congenital heart defects and determine the effects of micronutrient supplementation on the clinical, electrocardiographic and echocardiographic parameters.

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