Environmental and Physiological Barriers to Child Growth and Development

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Abstract

Aggregated analyses of child growth in low- and middle-income countries (LMICs) reveal a remarkably consistent picture of serious growth failure compared to the WHO reference growth curves. Impoverished diets with low dietary diversity are a key driver of poor growth, but there are important additional environmental factors that limit the uptake and utilization of nutrients. This paper considers such factors. A large proportion of the rapid growth deterioration in later infancy can be ascribed to infections and to wider nonspecific effects of living in an unhygienic environment, including the ingestion of toxins such as aflatoxin. Despite never revealing themselves as clinical syndromes, the great majority of children in rural low-income settings of Africa and Asia are antibody positive to numerous pathogens (CMV, EB, HepB, Helicobacter pylori, and many more) by 24 m; these infections must take their toll. Additionally, there is a syndrome widely termed environmental enteric disease that combines gut leakage with a chronic inflammation leading to nutrient losses and cytokine-mediated growth retardation. Systemic inflammation also inhibits nutrient uptake and utilization. Elimination of these environmental barriers will be key to achieving optimal child growth and development in LMICs.

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Introduction

Multicountry analysis of child growth in low-income countries reveals a remarkably consistent picture of serious growth failure compared to the WHO reference growth curves [1]. Birth weight is generally lower by 0.5–1.0 Z-score. Young infants then grow reasonably well until about 3 m postpartum when they enter a period of precipitate decline compared to the WHO reference, such that population averages often reach –2 Z-scores and worse in the second year of life. By 24 m, this decline halts, and in many settings, there follows a period of gradual catch-up. Data from rural Gambia shown in Figure 1 reflect these trends and extend the analysis into adulthood [2].

The low birth weight often seen in poor populations, especially in Asia, can be ascribed in part to small maternal size that reflects the environmental effects in prior generations. Possible epigenetic mechanisms that might mediate these intergenerational effects are discussed by Silver elsewhere in this symposium [3].

After birth, young, fully breastfed infants tend to thrive for the first few months and often reclaim some of the deficit with which they were born. The subsequent growth faltering is caused in part by poor diets with low dietary diversity and by the consequent deficiencies in a wide range of nutrients, but this is not the only factor. The aim of this chapter is to highlight some of the additional environmental factors that create barriers to healthy child growth and development by impairing the utilization of nutrients. The effects of clinical infections are well known and have been extensively summarized elsewhere so are not reprised here [4]. Instead, we cover one well-known factor, namely, the effects of chronic environmental enteric disease (EED), and 3 lesser-known factors. The first of these relates to the more insidious effects of children’s exposures to a wide range of pathogens that rarely, or never, manifest as clinical syndromes. The second is a summary of evidence about the effects of aflatoxin exposure on child growth. The third topic considers the effects of persistent low-grade systemic inflammation on nutrient uptake and utilization. The effects of dysbiosis of the gut microbiome are covered elsewhere in this volume [5].

The Possible Effects of “Silent” Subclinical Infections

A proportion of the rapid growth deterioration seen in later infancy and in the second year of life in low- and middle-income countries (LMICs) settings can be ascribed to overt infections such as diarrhea, malaria, and pneumonia. Par-
ents recognize the effects of such illnesses and seek medical care if available. Mothers in particular note the effects of such illnesses on their child’s appetite. But there is a second category of infections whose possible impact on appetite and nutrient utilization is rarely considered. These “silent” subclinical infections rarely reveal themselves as clinical syndromes. Yet, the majority of children in rural African settings are antibody positive to numerous pathogens (CMV, EB, HepB, *Helicobacter pylori*, and many more) by their first birthday. For instance, the prevalence of *H. pylori* infection in a study we conducted in rural Gambian infants was 56% at 12 months, but incidence rates were higher with some infants clearing their infection and then becoming reinfected [6]. CMV infection rates are notoriously high in young LMIC children, and this can be exacerbated by exposure to HIV [7]. The metabolic sequelae of these silent infections are unknown, but they must surely take their toll on metabolism and may have additional effects on the hormonal pathways regulating growth.

**Environmental Enteric Disease**

Additional to these silent infections and possibly related in part is a silent syndrome widely termed EED (Fig. 2) [8–11]. EED is a complex, common, and usually persistent damage to the gut mucosa. It combines villous atrophy with crypt hyperplasia, loss of tight junctions, and a chronic, nonresolving inflammatory infiltrate to the gut lining.

The etiology of EED is still not entirely clear and probably results from a constellation of factors all related to poverty and pooled under the label of water, sanitation, and hygiene (WASH). Pathogens causing diarrhea play a contribu-
tory (though not necessarily dominant) role [8]. As described by Robertson in this session [5], alterations in the gut microbiota reflecting an inappropriately slow maturation toward the normal postinfancy profile [12] and/or a frank dysbiosis [5, 13] each may play an additional role.

The features of EED combine to cause nutrient malabsorption, nutrient leakage and losses, metabolic wastage in fuelling the chronic inflammation, and translocation of whole bacteria or their inflammatory debris. It is likely that these all conspire to drive cytokine-mediated growth retardation [7].

Aflatoxin Exposure

Aflatoxins represent a range of carcinogenic toxins produced primarily by Aspergillus fungi that grow on poorly stored grains and seeds especially in hot and humid tropical climes. Early-life aflatoxin exposure is an important risk factor for cancers, especially liver cancer in later life. Aflatoxin can also be immuno-suppressive at high doses and there has been much interest in its possible impact on child growth, an impact that has been frequently demonstrated in animal studies.

Human observational studies have frequently shown an association between aflatoxin exposure and poor growth [14, 15] including in longitudinal analyses where, for instance, high maternal blood levels of aflatoxin adduct (a measure of
persistent exposure) have been associated with slower growth in the offspring [16]. The plausibility of such a link has been reinforced by a recent study showing that epigenetic methylation patterns of certain genes in the growth axis (including insulin-like growth factor 1) measured in infants are correlated with aflatoxin levels in their mothers’ blood during pregnancy [17]. However, all of these associations might be caused by confounding whereby poorer families have both higher exposure to aflatoxin and poorer growth in their children. It is also noteworthy that not all association studies show a linkage and one even shows a reverse association, thus emphasizing that we do not clearly understand whether aflatoxin does have direct effects on child growth. Randomized controlled intervention trials of aflatoxin reduction will be needed to clarify this picture, and, notably, a recent trial has reported a null effect on growth despite success in reducing aflatoxin exposure [18].

Notwithstanding a lack of definitive proof linking aflatoxin exposure to child growth, there is every reason to support efforts targeted at aflatoxin reduction and strategies such as biocontrol of the Aspergillus fungus show great promise.

**Chronic Low-Grade Systemic Inflammation**

Micronutrient deficiencies, which can impact on growth, and especially iron deficiency leading to anemia, can also be caused in some part by infections that impair both absorption and utilization of nutrients. Recent evidence suggests that a role for low-grade inflammation may be especially critical. The stress of birth is associated with a sharp and sort-lived increase in inflammation and then young infants generally display few signs of any inflammation. However, indicators of inflammation such as C-reactive protein and alpha-1 glycoprotein rise progressively in infancy in most LMIC populations. In rural Gambia, we have reported that, in different studies, 20–45% of infants over 2 months have C-reactive protein levels >5 mg/L and up to 80% have alpha-1 glycoprotein levels showing recent infection [6, 19].

The mechanism by which inflammation can cause a micronutrient deficiency has been most clearly demonstrated for iron where, in the presence of an infectious threat and/or the related inflammation, the iron-regulatory hormone hepcidin is upregulated by IL6 [20]. This blocks iron absorption in the duodenum and reduces circulating iron by locking it away in reticuloendothelial macrophages [20]. Recent evidence shows that many children living in a poor environment have persistently raised levels of hepcidin and that these elevated levels are driven by even very low-grade inflammation [21]. The source of this inflammation is still unclear, but it is apparent that respiratory infections are one im-

important cause, leading to the novel and unexpected insight that inflammation in airways epithelia might be an important driver of iron deficiency and its consequent anemia.

**Thresholds of Environmental Hygiene That Must Be Attained to Normalize Child Growth**

An obvious conclusion arising from the above description of the diverse nutrition-sensitive contributors to poor child growth and development is that optimal growth will only be achieved within an optimal environment. Elsewhere in this volume, Humphrey summarizes the very disappointing results of recent WASH interventions that have endeavored to create such an environment [22]. Our own analysis of child growth in families across a very broad gradient of socioeconomic status and housing conditions suggests that there is a very high threshold of hygiene that must be reached before children will be free from the environmental inhibitors of adequate growth described in this paper [23]. This reinforces Humphrey’s call for the so-called “Transformative WASH” solutions.

**Future Prospects**

The rapid decline in stunting and anemia rates seen in many South American countries in the past 3 or 4 decades has been well documented, especially in Brazil, where it seems clear that concerted efforts involving improved water and sanitation facilities, improvements in breast-feeding rates, poverty reduction, and mothers’ education have all contributed to the excellent progress seen. Thus, we can be optimistic that the global metrics on childhood malnutrition will drastically improve as countries pass through the economic transition (albeit with a risk of overweight and obesity). The evidence presented here emphasizes the need for holistic approaches that encompass a wide range of environmental improvements in addition to nutrition-specific interventions.

**Disclosure Statement**

The author received travel support and an honorarium from the Nestlé Nutrition Institute (NNI) for this meeting. The author is a Board Member for (NNI).
References


