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Implications of acquired environmental enteric dysfunction for growth and stunting in infants and children living in low- and middle-income countries

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Abstract

Changes in small bowel function early in infancy in developing countries are increasingly being demonstrated, probably accompanied by altered mucosal architecture in most individuals, including reduced enterocyte mass and evidence of immune activation and inflammation in the mucosa. These alterations appear to be the result of factors of uncertain nature in the environment, and may be a cause of growth faltering and stunting in young children. For these reasons, this constellation of findings is being referred to as environmental enteropathy, or as we propose herein, environmental enteric dysfunction. If the causes were known and effective interventions were available, strategies and policies to intervene at—or possibly before—birth could be developed and promoted in order to prevent subsequent malnutrition and recurrent infection, which are known to interact in a cyclical and synergistic manner in a downward clinical course often ending in death. Resources would be mobilized and applied differently, and the emphasis would change from treatment to prevention.

In order to move in this highly desired direction, investments in research will be required to establish the criteria to assess environmental enteric dysfunction, determine its predictive value for growth faltering and stunting, identify the causes, and propose and test potential interventions. The concepts and tools are available. What is required is the decision to move forward along this pathway to better health for infants and children in low-income countries.

Keywords

Biomarkers; infant nutrition; malabsorption; stunting

Introduction

In the past decade, interest in the role of altered small bowel histology and function in the pathogenesis of early childhood stunting and malnutrition has greatly increased. This is the result of several factors, including the continuing prevalence of stunting in young infants and children in developing countries [1, 2], despite many nutritional and healthcare interventions [3, 4], the introduction of new methods to assess intestinal function suitable for use in this age group, and some preliminary evidence that permeability of the small bowel to sugar substrates is, in at least a few pioneering studies, inversely correlated with growth (in both weight and height) in early postnatal life [5, 6]. These studies not only have noted the frequency of measurable intestinal absorptive dysfunction, but have provided evidence for a

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systemic and intestinal inflammatory response as an additional potential contributor to growth faltering and a potential target for interventions to interrupt its causative pathways [7].

The causes and consequences of an acquired intestinal dysfunction characterized by diminished capacity in tests of intestinal absorption and evidence of increased permeability of the intestinal mucosa, assessed by the lactulose:mannitol (or rhamnose) dual sugar absorption test [8], have been recently and thoughtfully reviewed by Prendergast and Kelly [9]. They emphasize that such an enteropathy may play an important role in the growth stunting so common in young infants in developing-country settings [5–7]. A better understanding of the causes and natural history of this enteropathy may lead to the development of effective interventions, significantly reduce early childhood malnutrition, reduce susceptibility to recurrent infections, promote growth and development, and improve child survival in developing countries. This analysis will summarize what we do and do not know about these very early alterations in intestinal digestive function, discuss their potential impact on childhood growth, and examine the policy implications for interventions to interrupt this pathway to stunting.

History

Around 50 years ago, it became possible to biopsy the small bowel mucosa of living individuals [10], and this was followed by a major revolution in the assessment of normal and abnormal mucosal structure. The Crosby–Kugler biopsy capsule [11] was the most used device at the time because it was easily swallowed and carried into the proximal small bowel by peristalsis, and when connected to a radio-opaque tube its position in the proximal small bowel could be confirmed by fluoroscopy or x-ray. Tissue suitable for gross and histologic examination was readily obtained. A smaller version was soon available that simplified biopsy in young children [12].

Studies of small bowel structure during the 1960s and 1970s identified a difference in the mucosal architecture between apparently healthy adults living in Western industrialized countries and adults native to and living in developing countries. The distinction was obvious on gross examination by means of a dissecting microscope, revealing a change from the predominant fingerlike villus structure of the gut in people from Western countries to flatter leaf and blunt villus forms in those from developing countries [13, 14]. This alteration resulted in a significant reduction in the villus-to-crypt ratio due to villus shortening and a concomitant reduction in the surface area of mature absorptive intestinal epithelial cells. Histological examination of the biopsies also showed increased numbers of inflammatory cells in the lamina propria, including lymphocytes and plasma cells [15]. Because these studies were conducted in tropical areas of the Caribbean [16, 17], Africa [18, 19], and Asia [20–22], the entity was originally named tropical enteropathy or tropical jejunitis. Expatriates moving to these countries and examined by serial jejunal biopsy after arrival developed similar morphological changes over time, sometimes associated with minor changes in stool consistency or pattern and some weight loss, but generally without any perceived illness [23, 24]. There were, of course, exceptions, and a few of the expatriates developed significant symptoms, such as chronic diarrhea and steatorrhea, including some

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with the typical course of tropical sprue [23, 25]. In one study, the intestinal changes in those with “asymptomatic” jejunitis reversed after the individuals returned home [25]. Similarly, small bowel morphology in a group of asymptomatic South Asian adults living in New York City became progressively more like that of the Western gut as the duration of time away from their original homelands increased [26]. Together, these studies suggested that these intestinal features were a response to some environmental factor present in the “tropics,” and that it was reversible by simply moving to a Western environment, presumably because the causative factor(s) was (were) not present there.

Nutrient malabsorption

D-Xylose

Using clinical tests of carbohydrate, fat, or vitamin absorption, most often the D-xylose absorption test, moderate reductions in function were readily documented in people in tropical countries and were acquired in westerners moving to these settings [19–21, 23, 24]. In one prospective study among American expatriates in Thailand, D-xylose absorption progressively diminished over time, reaching values that were similar to those found in asymptomatic Thai adults with biopsy-documented tropical enteropathy [27]. With a focus on small bowel functional rather than histological changes, the terms “tropical” or “subclinical” malabsorption began to be employed more frequently.

When studies were extended to children, it became apparent that the “lesion” of tropical enteropathy evolved soon after birth, although many fewer individuals with biopsy samples were available for analysis, particularly asymptomatic children without stunting, wasting, or a history of recurrent enteric infections. An important piece of evidence came from postmortem examinations of the small bowel from stillborn fetuses or neonates who died in the first few days after birth, which demonstrated normal-appearing, long, delicate villi in the jejunum [15, 28, 29]. Change in villus architecture to a flatter, more leaflike structure occurred during the first few months of life. The implication of these findings in very young infants is that some degree of malabsorption of nutrients might begin early in life and compromise nutritional status, contribute to stunting, and increase subsequent susceptibility to more serious intestinal infections. Once clinically evident malnutrition was present, these mucosal changes could be readily found in most of those affected. For example, in one study of 17 infants 12 to 36 months of age with kwashiorkor in Nairobi, Kenya, upper small bowel biopsies were obtained with a pediatric Crosby capsule and compared with biopsies from infants investigated in the United Kingdom for a variety of intestinal symptoms [30]. The appearance of the villi under the dissecting microscope was skewed toward ridges in the former and fingerlike villi in the latter, and 16 of the 17 malnourished children had increased lymphocyte infiltration within the lamina propria, compared with just 1 of the 15 UK control infants. A more recent study of 41 Zambian infants with kwashiorkor or marasmus, with a mean age of 17 months, revealed reduced villus height, increased crypt depth, and significant inflammation in the lamina propria, independently of HIV status [31]. In another study of 57 Indian children with chronic diarrhea aged 1 to 5 years, 86% of whom were diagnosed with protein–energy malnutrition, abnormal jejunal histopathology was present in

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73%, with 57% showing villous atrophy and mononuclear infiltration in the lamina propria [32].

In a study focusing on absorptive capacity using the D-xylose test, Bangladeshi infants and children from 2 to 64 months of age averaged approximately two-thirds of the value among control children studied in the United States across the whole age range, and lower values were associated with poorer growth [33]. In another study, half of a sample of clinically healthy rural Thai children aged 2½ to 9 years had D-xylose test results below the threshold of normal [34]. Among 70 Liberian children 5 to 13 years of age, 29% had low xylose excretion, compared with 0% among 14 children of American missionaries living in the country [35]. These studies document the high frequency of D-xylose malabsorption in young infants and children living in developing countries.

Intestinal permeability

The more recent development of dual sugar absorption tests has provided a method of simultaneously assessing gut barrier function and intestinal absorptive capacity in children in developing countries [36]. This test is conducted by administering a mix of lactulose, a disaccharide that is not absorbed across an intact small bowel mucosa, and mannitol or rhamnose, monosaccharides that are absorbed by normal mucosa but not subsequently metabolized in the body. Measuring the amounts of the two sugars present in serum or in urine to determine the ratio of the absorption or excretion of the two substrates (L:M or L:R ratio) provides an estimate of permeability, whereas mannitol or rhamnose absorption reflects carbohydrate absorptive capacity [37].

Studies conducted among children in Africa [38], Asia [39], and South America [40] have reported elevated L:M ratios relative to UK reference values, indicating an increase in permeability of the small bowel. This was found in asymptomatic children recruited from communities (i.e., not from clinical settings), as well as in those with diarrhea. Moreover, an inverse association between L:M ratio and height-for-age [41] or height gain [42] was found in some, but not all, studies [43]. Abnormal permeability was also reported in 36% of Aboriginal children without diarrhea investigated in Australia, in contrast to none of a group of non-Aboriginal control children [44]. Although there was variability among the results in different reports, some of this could be due to differences in how patients were selected (e.g., inclusion or exclusion of breastfed babies) or prepared prior to testing (e.g., fasting or not fasting), the dose of sugar administered, postchallenge collection and detection methods, and even how results are reported (e.g., as arithmetic vs. geometric means). This suggests the potential to improve the reproducibility and value of the L:M ratio as a diagnostic test.

A number of factors have been proposed to underlie altered function of small bowel mucosa, including a combination of microbial contamination of water and food [14], overgrowth of microbes in the normally relatively sterile proximal small bowel [19], constant exposure to nonpathogenic as well as known pathogenic microbes or bacterial components such as lipopolysaccharide (LPS) endotoxin [45], or the ingestion of unidentified immunologically active or toxic organic or inorganic contaminants present in water or food [46]. The evidence for an inflammatory response in the small bowel and the potential role of microorganisms or immunologically active molecules such as LPS has suggested that the

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acquired abnormalities are a T-lymphocyte–mediated process, based on studies of small intestinal biopsies from Gambian children, most of whom were malnourished and had diarrhea [47–49]. These studies have revealed increases in the number and altered phenotype of intraepithelial T cells, increased expression of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interferon gamma (INF-γ), and a decrease in regulatory cytokines such as transforming growth factor beta (TGF-β), with the most malnourished children having the most proinflammatory profile [49]. In addition, reductions in B cells and antibody-producing plasma cells correlated with the degree of malnutrition, which could have significant implications for host defense against enteric pathogens.

Implications of these findings

The evidence presented, *in toto*, strongly indicates that a spectrum of change in the histology and function of the small bowel occurs across the entire age range of individuals living in developing countries, in which environmental hygiene is generally poor. We suggest that this entity is best referred to as environmental (meaning acquired) enteric dysfunction (to focus on the functional alterations). In young infants and children, environmental enteric dysfunction may precede and dispose to malnutrition of varying degrees, which in turn contributes to an increased incidence of infectious disease, especially diarrhea. Malnutrition and enteric infection further alter mucosal structure and function and are known to promote a vicious cycle wherein infection worsens nutritional status, and malnutrition increases susceptibility to and severity of infections. We postulate that environmental enteric dysfunction and its functional consequences leading to poor absorption and utilization of food result in early stunting and are important risk factors for more severe clinical outcomes when episodes of clinical diarrheal disease occur. If this reasoning is correct, then identifying the causes of environmental enteric dysfunction and potential interventions to prevent its occurrence could reduce stunting, micronutrient deficiencies, poor development, including cognitive function, sequential infections, and early mortality and improve the long-term human potential in those surviving to adulthood [50].

Although the initial descriptions of environmental enteric dysfunction were based on examination of biopsies of the small bowel in adults, supplemented by available tests of intestinal absorptive capacity, there are serious ethical challenges to proposing single, let alone serial, biopsy of the gut in very young infants without evidence of a clinical illness for which biopsy is a useful diagnostic procedure. These considerations include the critical research need for biopsy very early in life, before manifestations of environmental enteric dysfunction occur, so that temporal events and correlations with potential causative factors can be assessed; the uncertainty of whether or not parents or legal guardians would generally consent to endoscopy and biopsy of very young, apparently healthy, infants, which would impact the possibility of obtaining an unbiased study cohort; and the likelihood that an ethical review committee would impose a requirement for a more medically sophisticated setting in which anesthesia and endoscopic biopsy could be safely performed and where necessary care could be provided in case of an adverse event. The latter constraints would make it virtually impossible to work in a field setting and thus would diminish the chances of obtaining serial biopsies from study participants.

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The ethical perspective also depends on whether biopsy of “healthy” children is considered to involve at least a minor increase above minimal risk, since this would mandate that a determination be made whether the knowledge to be gained was sufficiently valuable to improve the understanding and management of conditions affecting children to tolerate the added risk to the individual [51]. Anesthesia carries a low but not insignificant risk, and a recent review has concluded that general anesthesia is safer and more effective in providing comfort and amnesia than is intravenous sedation, reinforcing the need for appropriate facilities for endoscopy [52]. The principal serious direct complication of endoscopic biopsy is an obstructing hematoma of the small bowel, which has an incidence of approximately 1 per 1,000 endoscopies in children [53]. Vitamin K deficiency in children with malabsorption of fat, which is not usually assessed in the typical battery of functional studies, might exacerbate the risk of bleeding during endoscopy in a developing-country setting and would necessarily complicate the discussion of risk when obtaining informed consent [54].

Arguably, single biopsy studies would limit the scientific value of the procedure and make it more difficult to determine whether the benefit:risk ratio was sufficiently high to permit approval of the study design. Serial biopsies would increase the likelihood of interpretable results but expose the subject to multiple procedures. There could be a difference in the way different local ethical review committees at the study sites would approach the benefit:risk issue, itself a complication for such studies, whereas ethical review committees at collaborating institutions from high-income countries might well be more uniformly restrictive. Single biopsies at various times in individual subjects would be more likely to be approved but would provide limited insights into the causes, progression, and consequences of environmental enteric dysfunction. Serial samples, which would be of greatest scientific value, would no doubt be more problematic for institutional review boards to approve. These considerations have led us to conclude that a definition of environmental enteric dysfunction will need to rely on biomarkers alone, without biopsy data to connect functional and structural changes.

At this time, we can state with confidence that a significant proportion of infants living in low-resource poor countries experience growth faltering in early childhood, although the timing and extent of the problem will vary from country to country. When tests of small bowel function are conducted, some proportion of the infants will be found to have subnormal test results. Were small bowel biopsy to be performed, particularly in children already clinically malnourished or with acute or chronic diarrhea, it is likely that enterocyte mass would be reduced because of changes in villus structure from fingerlike forms to a flatter leaf-like morphology and a concomitant reduction in the crypt:villus ratio. We do not know the proximal causes of these structural changes, nor whether or not early subclinical alterations precede clinical malnutrition and diarrheal disease, and therefore whether or not they are involved in the progression from subclinical to clinical manifestations. Without this information, it is not possible to propose rational interventions specifically designed to interrupt the critical pathway of pathogenesis in order to maximize the cost:benefit impact of such investments.

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Toward a clinical and public health definition of environmental enteric dysfunction

If the analysis concerning the ethics of intestinal biopsy in young infants without clinical manifestations that provide a rationale for the procedure is accepted, the next challenge to be faced in the diagnosis of environmental enteric dysfunction is the reality that there is no single well-validated biomarker presently available to define environmental enteric dysfunction.

Although a number of new possibilities have emerged in recent years, none are consistently altered in the setting of environmental enteric dysfunction, possibly because the causative factors differ among individuals or in particular geographic settings, or because the response of the host is variable with respect to the functional parameters affected. A feasible, standard, and ethical way to define environmental enteric dysfunction is essential to document its association with early gut functional or mucosal changes in young children, to identify the likely causes, and as a prelude to proposing and testing interventions to prevent environmental enteric dysfunction in the first place. Ideally this definition should also be useful for retrospective analyses of previously published studies, that is, it should include criteria that have been frequently used in the past, as well as employ newer markers to guide studies still in the planning phases. Furthermore, because we have kept in mind the proposition that immune activation in environmental enteric dysfunction is an adaptive response to the environment and therefore in its earlier stages might provide protection against some infections, albeit at the cost of diminished nutrient absorption, the proposed interventions must not themselves lead to additional adverse health or nutritional outcomes.

To accomplish this goal, we recommend that a battery of old and new tests be employed that collectively assess intestinal absorption and permeability, enterocyte mass, inflammation, and microbial translocation and immune activation. Ideally, multiple test substances could be simultaneously administered without causing osmotic diarrhea as a side effect, with a sampling strategy to include blood, breath, and urine to gain maximum information at one time. These data would need to be evaluated as predictors of growth faltering, and once identified, the most sensitive and specific could be selected for general use, most likely a combination of markers to assess the different functions likely to be affected.

Nutritional consequences of environmental enteric dysfunction and assessment of growth

Multiple studies demonstrate the continuing problem of stunting, and to a lesser extent wasting, in young infants and children as a consequence of impaired nutritional status [55]. These manifestations are generally assessed by standard anthropometric measurements and reveal that an abnormal deceleration of growth in many developing-country settings begins in the first year of life, and is recognized as a problem in a substantial proportion of young infants and children by 2 years of age, and in some settings by 1 year of age or even earlier [56]. Because we are concerned that inadequate nutrient assimilation is a consequence of environmental enteric dysfunction acquired early in life, it is essential to begin studies to

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assess this relationship starting at birth or the immediate postnatal period at the latest, when most infants in developing countries are still breastfeeding and before significant postnatal growth faltering begins. Studies must also be initiated during this period if we are going to be able to determine the extent to which environmental enteric dysfunction is a cause or a consequence of, or is exacerbated by, malnutrition, ultimately leading to the cyclic interaction of malnutrition and repeated infectious disease episodes, especially diarrhea. This approach is supported by the results of a recent study of malnourished and nonmalnourished Bangladeshi infants 6 to 24 months of age who received different nutritional or support interventions, in whom improvement in L:M ratio test results were related to weight gain, regardless of the intervention [57].

In addition, because the usual anthropometric growth indicators (weight-for-age, height- or length-for-age, and weight-for-height or -length) are primarily useful to assess population growth and are biased toward identifying the most severely affected individuals when used in either a clinical or a research context, they do so after the most profound consequences have already occurred (crossing of z-score thresholds that are 2 or 3 standard deviations below the mean). A more useful and sensitive way to assess individual infants' growth performance is likely to be the determination of interval growth velocity in comparison with international standards. This approach should, at least to some extent, control for birthweight and individual genetic or familial variability in physical size. Measures of growth velocity and growth faltering are likely to be early indicators of adverse nutritional consequences of environmental enteric dysfunction when assessed among individuals in longitudinal cohorts. Such evaluations are critical to determine the impact of environmental enteric dysfunction and interventions on growth outcomes. In addition, use of growth monitoring and growth velocity assessments, by pinpointing the time frame when altered growth is first detected, may also provide insights into precipitating factors in the preceding weeks and pinpoint how the host has responded. While intestinal dysfunction of sufficient magnitude will ultimately affect attained size if it has significant nutritional consequences, measures of z-score thresholds would only elucidate this effect after significant injury and time has elapsed. We conclude that the validation of a functional definition of environmental enteric dysfunction is an important prerequisite to identifying strategies and policies to monitor growth and to intervene to prevent or reverse the earliest evidence of nutrient malabsorption before growth faltering becomes prominent as a harbinger of the vicious cycle of malnutrition and infection.

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