

Nutrition in Pediatric HIV Infection: Setting the Research Agenda

Gastrointestinal Tract Function and Malnutrition In HIV-Infected Children¹

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ABSTRACT Poor growth and/or weight gain was identified in the initial reports of children with AIDS (Oleske et al. 1983, Rubinstein et al. 1983). However, in the past 12 years little progress has been made to understand the mechanisms for these observations. Data from the NIAID/NICHD multicenter Women and Infants Transmission Study (WITS) demonstrated that a decline in weight occurred in the first four months of life followed by decreased linear growth (Rich et al. 1993). In older children weight and height seem to decline in parallel (McKinney et al. 1993), but loss of lean body mass may occur prior to a decline in weight (Miller et al. 1993). Adequate caloric intake can improve weight gain, but has little effect on height velocity and lean body mass (Henderson et al. 1994, Miller et al. 1992). Long-term survivors with HIV infection are shorter than anticipated, and these changes cannot be explained solely by inadequate nutrition or by endocrine abnormalities. The immune system, gastrointestinal tract function, malnutrition, and chronic or recurrent infection interact and contribute to the nutritional deficiencies and problems with growth observed in the HIV-infected child. *J. Nutr.* 126: 2620S-2622S, 1996.

INDEXING KEY WORDS:

- HIV infection • gastrointestinal function
- growth • immune function • malnutrition

GASTROINTESTINAL TRACT FUNCTION

The gastrointestinal tract is a central element in the acquisition of HIV disease, the development of failure to thrive, and the immune deterioration that develops with disease progression (Winter and Chang 1993). Although some children may become infected with HIV in utero, the majority seem to acquire the infection perinatally. The route of infection is not known, but

the skin, mucous membranes, and gastrointestinal tract are good candidates for tissue across which HIV can migrate. Although the gastrointestinal tract is the largest immunologic tissue, little is known about infection of mucosal lymphoid elements by HIV in the neonate. However, one can speculate that virus crosses the epithelium and enters the lamina propria where HIV infects lymphocytes or is taken up by macrophages. These HIV-associated cells then migrate to mesenteric lymph nodes which become a reservoir for virus in an analogous manner to that described in the peripheral lymph nodes (Fox and Cottler-Fox 1992).

During the asymptomatic period following exposure to virus, changes are most likely beginning to occur in the gastrointestinal mucosa simultaneously with the onset of changes in body composition (Rich et al. 1993). Although not well studied in the infant, IgA secretion is likely decreasing and the CD8+ lamina propria lymphoid population is increasing. These immunologic events may contribute to the development of bacterial overgrowth in the proximal small intestine and the absorption of bacterial products (e.g., endotoxin) which can activate the mucosal immune system and potentially enhance viral replication. The effects of

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these events on epithelial cell function are not known, but we and others have observed that HIV-infected children develop lactose intolerance earlier than predicted based on race or age (Miller et al. 1991). The mechanism for this clinical observation is not known, but lactase and sucrase specific activities and expression of lactase mRNA should identify the pathogenesis of alterations in lactase biosynthesis. The impact of these changes of intestinal function on body composition is not known, but, early in life, HIV-infected children begin to increase fat mass at the expense of lean body mass.

As children become more symptomatic, malabsorption, diarrhea, decreased oral intake, and enteric infections become more common and growth is altered. Many enteric infections that are found in HIV-infected adults are rare or not reported in the pediatric population (Lewis and Winter 1995). *Isospora belli*, *Microsporidium*, *Entamoeba histolytica*, coronavirus, and calicivirus have been reported in adults, but not children (Lewis and Winter 1995). However, *Cryptosporidium parvum*, *Giardia lamblia*, *Mycobacterium avium-intracellulare*, *Clostridium difficile*, *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., Cytomegalovirus, Adenovirus, rotavirus, and Herpes simplex virus have been found to be enteric pathogens in the pediatric population (Lewis and Winter 1995).

The interrelationship between malabsorption, malnutrition, immune deficiency, and enteric infection causes a cycle that potentiates the growth problems of HIV-infected children. Intestinal epithelial cell dysfunction and possibly bacterial overgrowth result in nutrient malabsorption and, if supplemental calories are not provided, eventual malnutrition. Protein energy malnutrition without HIV infection can result in immunologic abnormalities including decreased T-cell number, diminished CD4 number, impaired delayed hypersensitivity, elevated serum immunoglobulin levels, and impaired specific antibody responses (Beisel 1996). When these same abnormalities are found in HIV-infected children, one cannot determine if they are related to HIV infection or to malnutrition. The similarities in immune dysfunction between malnutrition and HIV infection suggest that malnutrition could potentiate the immunologic dysfunction of HIV disease.

FAILURE-TO-THRIVE

Failure-to-thrive is reported in approximately one-third of HIV-infected children and is associated with decreased survival (Thea et al. 1993). In infants born to HIV-infected mothers, a decreased rate of weight gain occurs in the first four months of life prior to a decline in the rate of linear growth (Rich et al. 1993). In long-

term survivors the decreased rate of growth continues and may be associated with decreased lean body mass.

Causes of nutritional deficit leading to malnutrition can be divided into three broad areas: diminished nutrient intake, increased nutrient losses, and increased nutrient requirements. Decreased nutrient intake can be caused by esophagitis, problems with chewing, oral ulceration, nausea, vomiting, dysgeusia associated with zinc deficiency or drug therapies, fever, pain, dementia, depression, and/or despair. Increased nutrient losses are most commonly caused by opportunistic infections, but lactose intolerance, pancreatic insufficiency, or small intestinal injury can contribute to malabsorption. Increased nutrient requirements are most frequently associated with febrile illnesses, but metabolic abnormalities such as futile cycling and abnormal hormone or cytokine production can alter intermediate metabolism and modify nutrient requirements. Data supporting these phenomena in HIV-infected patients come primarily from studies in adults; few studies have systematically addressed these issues in pediatric HIV infection. For a review of these relationships see Raiten (1991).

Social factors in countries where food supplies are less available than in North America and Europe contribute significantly to infant survival in the HIV-infected population. Maternal health is one of the most important determinants in predicting whether or not a child will survive (Thea et al. 1993). If an HIV-infected child's mother becomes ill with fever, weight loss, or diarrhea and cannot care for her baby, that child's risk for mortality is greatly enhanced (Thea et al. 1993). The risk is increased further if the mother dies.

There have been many strategies to reverse and prevent the loss of weight and lean body mass that occurs in HIV-infected individuals (Grunfeld et al. 1992). Appetite stimulants such as megestrol acetate (Megace®), and dronabinol cause increased weight, but little increase in lean body mass in HIV-infected adults (Cat and Coleman 1994). Anecdotal experience in children suggests that these agents do not reverse growth retardation. Gastrostomy tube feedings in HIV-infected children can provide nutritional support for those children unable to ingest sufficient calories, but also appear to add fat mass at the expense of lean body mass (Henderson et al. 1994). Recent clinical trials of human growth hormone in adults demonstrated that nitrogen loss was diminished and that the weight gain resulted from increased lean body mass (Mulligan et al. 1993). If similar results can be obtained in children, a therapy that not only reverses the loss of lean body mass, but also potentiates growth will be available.

MODELS FOR FUTURE RESEARCH

Models to study gastrointestinal tract dysfunction and failure-to-thrive caused by HIV disease are needed.

Transplantation of human fetal intestine into athymic mice provides a human intestinal epithelium (Winter et al. 1991, Winter et al. 1992), but attempts at introducing a human mucosal immune system into the model have not been reported. Transgenic mice with deletions of specific regions of the HIV genome fail to grow (Klotman et al. 1995) and could serve as a model for growth retardation; however, the mechanism for failure-to-thrive in these mice may not be the same as the causes in infants. Nonhuman primates offer one of the best models to study the effects of SIV on the intestinal mucosal immune system, but the supply of these animals is limited and they are expensive to purchase and maintain. Infection via the amniotic fluid offers a similar model to that of the human, but tissue sampling in the monkey will permit prospective evaluation not possible in humans. Together these models will enable investigators to determine the pathobiology of HIV in the gastrointestinal tract and the reasons for malabsorption, malnutrition, and growth retardation.

GAPS IN KNOWLEDGE

Many questions exist in our knowledge of gastrointestinal tract function and nutrient utilization in HIV-infected children. These include: (1) will early nutritional intervention prevent delayed growth in HIV-infected infants; (2) will maintenance of normal nutritional status delay progression of immune dysfunction; (3) what is the role of decreased lean body mass in progression of HIV-induced disease; (4) what is the relationship of gastrointestinal epithelial cell and mucosal immune function to disease progression; (5) what role, if any, do cytokines play in the abnormal growth observed in HIV-infected children; and (6) are problems relating to growth reversible by nutritional and/or pharmacologic therapy?

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