
INVITED PAPER

Chronic Diarrhoea in Protein-Energy Malnutrition

by

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Introduction

Infection and malnutrition exemplify synergistic role of these two major factors in the pathogenesis of diarrhoea in protein-energy malnutrition.

Gastrointestinal Infection

Specific intestinal pathogens are sometimes identified as causing attacks of childhood gastroenteritis and chronic diarrhoea but most reports from non-tropical regions indicate a low yield from stool cultures. However, enteric pathogens particularly *Shigella*, *E. coli*, *Salmonella* and *Campylobacter* are isolated much more readily from children with chronic

diarrhoea in developing countries, presumably because of higher rates of exposure to these micro-organisms in contaminated environments.

Our understanding of the causes of chronic childhood diarrhoeal illnesses has been improved over recent years by the discovery of 'newer' infecting micro-organisms, particularly viruses and enterotoxigenic bacteria. This helps explain some of the largely negative results of earlier microbiological studies.

Enterotoxigenic Bacteria

Research into cholera and other watery diarrhoeas showed that some bacteria produce toxins which interfere with

intestinal fluid and electrolyte transport. Many mechanisms are involved including mucosal adherence and toxin production, particularly by strains of *E. coli*.

These bacteria produce either a heat-labile toxin (LT) or a heat-stable toxin (ST); some produce both.

LT resembles cholera toxin (CT) and shares with it some immunological activity. This is potentially important because it raises the possibility of control of at least some of these infectious diarrhoeas by immunization. It has also led to the development of reliable ELISA methods for identification of LT-producing bacteria. This has now largely replaced earlier laboratory animal methods such as the ligated ileal loop or cell culture systems which are useful only in places with sophisticated laboratory methods. With ST, identification is more difficult but the suckling mouse assay when used under carefully standardized conditions is reliable although not yet suited to general use under field conditions or in routine diagnostic laboratories.

The distribution of toxigenicity among intestinal bacteria is still undefined. Many strains of *E. coli* are known to be toxigenic and are now often referred to as ETEC. Other micro-organisms have been recognised in recent years as being toxigenic. They include *Shigella sonnei*, *Clostridium perfringens*, *Klebsiella* sp., *Staphylococcus aureus*, *Pseudomonas* sp. and even the yeasts, *Candida* sp. In recent studies in our own laboratory we have found that *Aeromonas hydrophila*

is commonly isolated from stool cultures from children with diarrhoea in whom no other enteropathogens could be identified. These *Aeromonas* sp. are toxigenic using several recognised assay systems including a gut perfusion model, the suckling mouse assay and some in vitro assays. Adequate epidemiological studies of the importance of enterotoxigenic bacteria in developing countries await the development of simple, reliable and portable diagnostic methods suitable for use under field conditions.

Viruses

Viruses have recently been recognised as a significant cause of acute diarrhoea in children in non-tropical and tropical regions but their possible role in causing chronic diarrhoea in protein-energy malnutrition is as yet unknown. Experimental viral gastroenteritis in animals causes extensive cytes lining the small intestinal epithelium and this leads to malabsorption of fluid, electrolytes of nutrients. It is possible that this type of damage may be significant as a contributor to the widespread problem of chronic diarrhoea in protein-energy malnutrition.

Intestinal bacterial flora in malnourished children

Several studies have shown that intestinal secretions from malnourished children obtained in vitro by per-oral aspiration have significant contamination

by large numbers of bacteria. Bacterial contamination of upper intestinal secretions is common in malnourished children but is not clinically significant. Bacterial overgrowth in the proximal gut can produce a wide range of clinical effects including steatorrhoea, carbohydrate malabsorption, hypoproteinaemia, vitamin B₁₂ deficiency and its associated macrocytic anemia and iron deficiency.

These effects are related to the bacterial degradation of bile salts affecting micellar solubilization of fat, damage to the function of mucosal enterocytes and bacterial binding of vitamin B₁₂.

In malnutrition these and other mechanisms may operate, particularly with recurrent and chronic gastrointestinal infections and infestations damaging the intestinal mucosa. Toxigenic bacteria, particularly species of *E. coli*, are likely to be especially important because of their prevalence in the gastrointestinal tract in malnourished children and their capacity to produce toxins which interfere with the intestinal absorption of fluid and electrolytes.

The gastrointestinal mucosa

There are significant differences between the appearances of the gastrointestinal mucosa in tropical and non-tropical regions; these are accentuated in children with protein-energy malnutrition. The changes include thinning of the gut wall, marked flattening and broadening of the intestinal villi, extensive inflammatory infiltration of the lamina

propria and alteration of the enterocytes from columnar to cuboidal or squamous.

Recent work has shown that the gastric mucosa is also abnormal in a small group of malnourished Indonesian children. Chronic gastritis was present in most of them and was associated with reduced levels of resting gastric acid secretion and very marked impairment of the responses of the gastric mucosa to stimulation by the hormone, pentagastrin. Secretion of hydrochloric acid is one of the normal factors controlling the upper intestinal microflora and the loss of this mechanism in malnutrition could contribute to the heavy bacterial populations found in the upper gut in malnourished children as mentioned above.

Gastrointestinal function

It has been known for many years that intestinal function is impaired in malnutrition but our understanding of the basic underlying mechanisms remains inadequate. For example, increased faecal losses of nitrogen has been well documented but the possible contributions of impaired digestion and absorption, increased mucosal and trans-mucosal losses and the role of intraluminal factors are uncertain. Fat absorption is also impaired in malnutrition but it is difficult to assess because when the fat balance is done during the early days of treatment the amount of fat ingested is usually very small or, alternatively, balances are performed when recovery

is progressing well and intestinal function presumably improving.

Steatorrhoea in malnutrition may be related to impaired micelle formation due to depletion of the bile salt pool but may have other underlying causes, such as decreased intraluminal lipolysis, from depression of exocrine pancreatic secretion or defective betalipoprotein production before transport of fat into lymph.

Carbohydrate intolerance and malabsorption is of major importance in chronic protein-energy malnutrition. The early studies from Africa clearly established this and they have been repeatedly documented from many centres since the 1960's. Carbohydrate malabsorption may be so severe as to be life-threatening, causing severe dehydration and metabolic acidosis in association with temporary monosaccharide malabsorption. This may be related to bacterial overgrowth of the upper intestinal contents leading to bile salt deconjugation which damages the energy-dependent transmucosal active sugar transport mechanisms and the ultra-structural components of the enterocytes.

Alternatively, it may be related to the effects of bacterial enterotoxins in the gut lumen affecting the mucosa. These effects on the intestinal mucosa may be quite extensive and involve water-soluble nutrients, such as monosaccharides and amino acids. The damage which occurs so commonly in the upper intestinal mucosa in protein-energy malnutrition is very important clinically because

of the important digestive function of the brush border part of the enterocytes.

Disaccharidase deficiency is therefore very common in malnourished children with diarrhoea and occurs in about 25% of patients in most reported series. This has important implications when planning nutritional rehabilitation programmes. Secondary sugar intolerance is very common in malnutrition and must be taken carefully into account when advising dietary treatment but it is dangerous to recommend ceasing breast-feeding unless lactose intolerance is very severe. There are variable effects on intestinal electrolyte transport in malnutrition which is affected by abnormal intermediary metabolism and geographical differences in dietary intakes of the minerals. Vitamin and haematonic deficiencies are also important and have significant geographical variations.

Rickets is a problem in large urban areas in countries where the custom is to cover the child from the sun, such as in Ethiopia.

Vitamin E deficiency is believed to contribute to the anaemia of protein-energy malnutrition, for example, in the Middle East and Thailand.

Anaemia occurs in about 10% of children with chronic protein-energy malnutrition and may be related to folic acid deficiency. Vitamin B₁₂ deficiency has also been reported with megaloblastosis. Iron deficiency is very common but is often related to other causative factors,

such as malaria or hookworm infestation.

The effects of protein-energy malnutrition on the intestinal mucosa are very diverse and clinically very significant. They contribute importantly to the problem of chronic diarrhoea in children with protein-energy malnutrition and must be taken into account in therapeutic and dietary treatment of affected children. There are still large gaps in knowledge of the effects of protein-ener-

gy malnutrition on the gastrointestinal mucosa. These include details about the contribution of malabsorption to nutrient and caloric wastage from the gastrointestinal tract and finer details about best methods for nutritional rehabilitation.

These will probably depend in most places on the prevailing local circumstances, beliefs, customs and availability of local foods.