Tropical sprue in southern India

V. I. Mathan  The Wellcome Research Unit, Christian Medical College Hospital, Vellore 632 004, India

Abstract

Tropical sprue, a primary malabsorption syndrome affecting residents and visitors to several tropical regions, occurs in southern India in endemic and epidemic forms. The stomach, the small intestine and colon are affected and malabsorption results in nutrient deficiency. Enteroctye damage, the primary lesion in southern Indian tropical sprue, is the result of a persistent lesion of the stem cell compartment. This lesion occurs on a background of tropical enteropathy and the available evidence suggests that an immunity conferring agent may be responsible for initiating the damage.

Introduction

The Charakasamhida, an Indian treatise on medicine written sometime between 600 and 1300 BC, has a chapter entitled “Graham Vyadi” or “Disorders of assimilation of food”. This clinical description of patients with chronic diarrhoea caused by “the failure of the digestive fire properly to burn ingested food” is probably the earliest account of tropical sprue and highlights the fact that this syndrome affects indigenous populations in tropical countries (Baker & Mathan, 1971). Tropical sprue became important because it was a major cause of morbidity and mortality in expatriates from temperate zones. Unfortunately the wide prevalence of this syndrome in indigenous populations was not appreciated and as late as the 1960s tropical sprue was considered mainly a disease of expatriates from temperate zones.

The initial studies supported by the Wellcome Trust at Vellore showed that almost all non-pregnant adults with megaloblastic anaemia, in southern India, had malabsorption syndromes (Baker, 1957, 1958). The detection of an epidemic of tropical sprue in 1961, and the demonstration that the small intestine in healthy southern Indians was, both structurally and functionally, different from that in apparently healthy residents in industrialized countries (Baker et al., 1962; Mathan & Baker, 1971; Baker & Mathan, 1972), led to the detailed studies during the last three decades which are reviewed in this paper.

The “normal” background

The surface architecture of jejunal mucosal biopsies, from healthy southern Indian controls, showed broad leaf- & tongue-shaped structures and long ridges often thrown into a convoluted pattern, but no finger-like villi (Baker et al., 1962). This morphological alteration was an acquired defect, since the foetal intestinal epithelium in India was the same as in temperate climates (Chacko et al., 1969). The architectural change was accompanied by increased thickness of crypts, increased infiltration of the lamina propria and the epithelium by mononuclear cells, and scattered degenerated enterocytes (Mathan, M. et al., 1975a). Similar morphological changes develop in laboratory animals (Baker et al., 1963) and it was shown that exclusion of a segment of bowel from luminal continuity prevented the occurrence of the lesion or even reversed existing changes (Chacko et al., 1968). Increased loss of functional enterocytes with accelerated cell turnover was responsible for these changes (Mathan, V. I. et al., 1982). The morphological abnormalities were associated with minor abnormalities of intestinal absorption, nearly half of the apparently healthy adults having malabsorption of d-xylose, 10% mild steatorrhoea and about 3% vitamin B12 malabsorption (Baker & Mathan, 1972). These morphological and functional changes in the small intestine in health have been designated tropical enteropathy and are likely to be an adaptation to the intestinal luminal environment (Mathan, V. I. et al., 1982).

Tropical enteropathy has been described from several tropical developing countries (Baker, 1973), but not from Singapore, which, although in the hot tropics, has environmental characteristics similar to the industrialized countries, with good nutrition, sanitation and water supply and a low incidence of acute diarrhoea. Among these environmental factors a consistent finding in southern India has been the isolation of bacterial enteric pathogens from the faeces of asymptomatic, apparently healthy individuals of all age groups (Rajan & Mathan, 1982; Mathan, V. I. & Rajan, 1986). In addition, the lumen of the small intestine as well as the mucosa is heavily colonized by both aerobic and anaerobic organisms (Bhat et al., 1972, 1980). The prevalence of enterovirus and parasite infections is also high in this population (Patel et al., 1984, 1985). These findings suggest that the luminal microbial flora may play a role in the pathogenesis of the changes of tropical enteropathy.

Abnormalities of the gut epithelium in apparently healthy individuals were not confined to the small intestine but occurred also in the colon (Mathan, M. & Mathan, V. I., 1985). Rapid turnover of colonocytes, with signs of cellular immaturity and non-specific injury resembling the transitional epithelium adjacent to colonic tumours, characterized tropical colonopathy.

The diagnosis of tropical sprue

Tropical sprue is a primary malabsorption syndrome of unknown aetiology affecting residents of, and visitors to, several tropical regions (Baker & Mathan, 1968; Wellcome Trust, 1971). The diagnosis in the individual patient necessitates the demonstration of intestinal malabsorption of at least 2 nutrients and the exclusion of diseases that can give rise to secondary malabsorption (Mathan, V. I., 1984). The diagnosis is complicated by the occurrence...
of tropical enteropathy and associated malabsorption. It has been suggested that tropical sprue is an "iceberg" disease, the symptomatic peak of tropical enteropathy. However, comparison of a group of patients with tropical sprue, and a control group with tropical enteropathy and malabsorption of single nutrients, showed that the two were different entities (Baker & Mathan, 1971). Until characteristic pathological lesion(s) or aetiological agent(s) are identified, tropical sprue, the result of damage to the intestinal mucosa by unknown factors, will remain a diagnosis of exclusion.

**Epidemiology**

Tropical sprue is endemic in many tropical developing countries and has been reported from Central and South America, the Caribbean islands and south and southeast Asia, but not from sub-Saharan Africa. In addition to endemic cases, epidemics of tropical sprue occur. During the second world war, in Assam and Burma, epidemics of tropical sprue were a major cause of repatriation of troops to UK. The Madras public health service also reported several epidemics with chronic diarrhoea. Of the 40 epidemics of diarrhoea studied during the last 26 years at Vellore, 7 were epidemics of tropical sprue, with patients developing malabsorption very early in the course of the illness and many patients continuing to have diarrhoea for periods longer than a month (Baker & Mathan, 1970; Mathan, V. I. & Baker, 1968, 1970, 1971; Mathan, V. I. et al., 1966). The epidemiological characteristics of epidemics of tropical sprue were distinctly different from those of epidemics of acute diarrhoea in this population. The attack rate was higher in adults than in children and the index case was usually an older person. The epidemic evolved over several months and new cases continued to appear for a year or more. The median case-to-case interval in families, during the first wave of the epidemic, was more than a month and secondary cases were usually younger people. Environmental or dietary factors could not be identified in the aetiology. Detailed bacteriological and parasitological studies and conventional virological studies failed to identify any aetiological agent. When villages affected by epidemics of tropical sprue were followed up for several years, secondary waves of the epidemic occurred. 5-6 years after the initial wave. In two such instances the attack rate for symptomatic illness was significantly higher in children, born after the first wave of the epidemic, than in adults living in the village at the time of the initial wave, suggesting that the agent which caused the epidemic had conferred some immunity.

Clinical features

Most patients with tropical sprue, both endemic and epidemic, present with chronic diarrhoea associated with anorexia, a feeling of abdominal distension and loud borborygmi. Apart from these primary gastrointestinal symptoms, the clinical picture is dominated by multiple nutritional deficiencies, anaemia, glossitis, stomatitis, cutaneous hyperpigmentation, oedema and skin and hair changes associated with hypoproteinaemia (Baker & Mathan, 1971). About 1% of patients with endemic tropical sprue may present without a history of diarrhoea but with features of nutritional deficiency only.

In southern India 98% of patients have steatorrhoea and xylose malabsorption and 65% have vitamin B12 malabsorption. The absorption of a variety of other nutrients, such as folate, iron, vitamin A, proteins and carbohydrates is also abnormal. Jejunal mucosal biopsies, careful radiological examination with small intestinal follow through, immunoglobulin estimation and quantitation of the luminal bacterial flora are among the investigations necessary to exclude secondary malabsorption. Commonly encountered conditions which give rise to secondary malabsorption in southern India include diffuse intestinal lymphoma, hypo- or agammaglobulinaemia with nodular lymphoid hypoplasia, the stagnant bowel syndrome (including intestinal tuberculosis), parasitic diseases and non-specific ulcerative colitis. These conditions account for less than 5% of all patients who have presented to this unit with a history of chronic diarrhoea and malabsorption. Abdominal tuberculosis with diffuse small bowel ulceration or multiple strictures and the stagnant bowel syndrome are particularly difficult to diagnose differentially. In the last 26 years the diagnosis of abdominal tuberculosis with malabsorption was confirmed in only about 40 patients, while over 2000 patients with tropical sprue were seen.

The natural history of the disease is characterized by remissions and relapses. Symptomatic remissions may or may not be associated with improvement in intestinal function. In epidemics 50% of patients have diarrhoea and malabsorption for longer than one month and about 15% for over a year.

The high prevalence of nutritional deficiency in the southern Indian population suggested that, if deficiencies were causal, their prevalence in the patients should be maximal at the onset of disease, while their severity could increase with increasing duration of malabsorption. In the large group of patients who have been followed up, the prevalence of deficiencies was lowest in patients ill for less than one month. The prevalence and severity of deficiency states increased significantly with longer duration of malabsorption. This clearly suggested that nutritional deficiencies were secondary to malabsorption in this disease. The severity of the epidemic also did not provide any evidence that nutritional deficiency was causal.

The propensity for spontaneous remissions makes the evaluation of therapeutic procedures difficult. Reports from the Caribbean islands and from the UK suggested that therapy with broad spectrum antibiotics, or vitamin B12 and folic acid, or all three together, was curative. However, the experience in southern India was different. The rate of remission and return of normal intestinal function, in a group of untreated controls followed up for similar periods of time, was no different from that of a group of patients given a 6-month course of tetracycline with or without folic acid and vitamin B12. In a few patients there was a dramatic response to tetracycline, occurring within the first 72 to 96 h of therapy, but even in these patients the response could not be linked to alterations in the intestinal flora.

In the rural areas of southern India untreated tropical sprue has a high mortality. The death-to-case ratio in the 1960-61 epidemic was 30 per 100. With maintenance of hydration, nutritional support and
symptomatic relief of diarrhoea, the mortality has been reduced to less than 1%.

**Pathophysiology**

**The stomach**

Hypochlorhydria or achlorhydria and defective secretion of gastric intrinsic factor associated with atrophic gastritis has a high prevalence in patients with tropical sprue (VAISH et al., 1965). In some patients, particularly the elderly, the gastric lesion may persist even after the intestinal lesion has recovered. Such patients may have defective vitamin B12 absorption, corrected by the administration of intrinsic factor, as the only evidence of malabsorption. While parietal cell antibodies can be demonstrated in most patients with tropical sprue, intrinsic factor antibodies are absent.

**The small intestine**

With the availability of peroral jejunal biopsy techniques the wide prevalence of jejunal mucosal lesions in tropical sprue was established. The lesion was non-specific, with abnormalities in the surface epithelium, increase in the thickness of the crypt, reduction in the villus length and marked mononuclear cell infiltration of the epithelium and lamina propria. Except for the extensive damage to enterocytes, these changes appeared to be only an amplification of the changes in tropical enteropathy. However, morphometrical studies showed that the severity of the mucosal morphological lesion can be quantitated and distinguished from the changes in tropical enteropathy (MATHAN, M. et al., 1986). The severity of the mucosal lesion correlated well with the severity of malabsorption.

Electron microscopic examination of jejunal mucosal biopsies established that enterocyte damage in the surface and crypt epithelium was the primary lesion. Extrusion of damaged enterocytes from all levels of the crypt-villus unit, rather than from the normal zone of extrusion at the villus tip, was a striking feature (MATHAN, M. et al., 1975a). Enterocyte damage, especially in the crypt or regenerative compartment, occurred early during the course of illness in epidemics. The increased lymphocytic infiltration in the epithelium (ROSS & MATHAN, 1981) was shown to be secondary to enterocyte damage (MARSH et al., 1984).

*In vitro* culture organ of jejunal mucosal biopsies, pulse labelled with tritiated thymidine, established that epithelial cell turnover and migration was increased in response to accelerated loss of cells from the epithelium. This enabled the development of a model of the pathogenesis of the small intestinal lesion in tropical sprue. The agent(s) causing tropical sprue damage(s) some of the enterocyte precursors in the stem cell compartment. The damaged stem cells give rise to damaged progeny which are extruded rapidly from the epithelium. The stem cell compartment increases turnover to replenish the loss of functional epithelial cells, giving rise to the characteristic, but nonspecific, morphological abnormality, with shortening of the villi and increase in the thickness of the crypt (MATHAN et al., 1986). A major question that needs to be answered is whether enterocyte damage in the stem cell compartment is unique to southern Indian tropical sprue.

**The colon**

Patients with tropical sprue in southern India do not have significant secretion or malabsorption of water in the small intestine (HELLIER et al., 1977). However, the capacity of the colon to absorb water and electrolytes was significantly impaired and some patients even had net colonic water secretion (RAMAKRISHNA & MATHAN, 1982). The extent of water malabsorption by the colon paralleled the amount of unsaturated free fatty acids in the stool (RAMAKRISHNA & MATHAN, 1986). Unsaturated free fatty acids inhibit the enzyme sodium potassium adenosine triphosphatase (Na-K-ATPase) *in vitro* (TIRIAPPATHI et al., 1983). Na-K-ATPase, located on the basolateral membranes of colonocytes, is the biochemical equivalent of the sodium pump. It is likely that the increased faecal excretion of unsaturated free fatty acids in tropical sprue inhibits the colonocyte Na-K-ATPase and contributes to diarrhoea and water loss. Morphological damage to colonocytes, similar to the abnormalities in the enterocytes, also occurs in tropical sprue. These structurally abnormal colonocytes could facilitate entry of unsaturated fatty acids from the colonic lumen, leading to inhibition of the Na-K-ATPase on the basolateral membranes.

**Aetiology of tropical sprue**

The aetiology of tropical sprue should explain the initiation and the persistence of intestinal damage. Nutritional deficiency, toxins and infections are the possibilities that have been investigated. If nutritional deficiency is causal, correction of the deficiency should revert the lesion — a situation not found in southern India. The pattern of the prevalence of nutritional deficiencies strongly supports the hypothesis that they are the result, but not the cause, of malabsorption. Nutritional deficiencies may modify the clinical course and delay the healing of the lesion, leading to delayed recovery or more severe illness. Detailed epidemiological studies in southern India failed to identify any dietary constituent that may be causal.

The occurrence of epidemics of tropical sprue, and the changing age-specific attack rate during the late waves of epidemics, suggest an agent conferring immunity. However, conventional microbiological and virological techniques failed to identify any agent. Direct electron microscopic examination of faecal samples from patients affected in epidemics during the last ten years showed the presence of virus-like particles, resembling the coronaviridae, tentatively designated coronavirus-like particles (CVLP) (MATHAN, M. et al., 1975b). While the prevalence of CVLP was very high in faecal samples from patients affected in epidemics of tropical sprue it is also high in unaffected control individuals. Attempts to cultivate CVLP *in vitro*, and to show a serological response in patients excreting CVLP, have been unsuccessful.

**Tropical sprue: a syndrome**

The clinical features and natural history of tropical sprue (WELLCOME TRUST, 1971) have been described from the Caribbean islands, British troops in Singapore and Malaysia, expatriates returning to the UK from India, and returned overland travellers from the UK to India and Nepal. Comparison of the disease in
southern Indian patients with published data from other areas suggests that the Indian disease may be different, or an expression of the same disease modified by environmental and nutritional factors. In the Caribbean islands patients with tropical sprue all have vitamin B12 malabsorption, respond promptly to broad spectrum antibiotics, and small intestinal colonization by toxin-producing coliforms appears to be aetiologically important. British troops in Malaysia developed the illness at the end of long patrols in the jungle and, during the acute phase, responded to folic acid therapy. Returned expatriates from India in the UK presented a more homogeneous population of patients with chronic symptoms, who invariably had vitamin B12 malabsorption and megaloblastic anaemia and needed broad spectrum antibiotics and folic acid in their treatment. Malabsorption in overland travellers appeared to have a mixed aetiology including parasitic infection and bacterial overgrowth, which was a reflection of their life style. Endemic cases of tropical sprue have been described from many centres in India and clinically they all appear similar. The early occurrence of enterocyte damage in the crypts, with persisting damage during the course of the illness, as a characteristic lesion in southern Indian epidemic tropical sprue patients, now raises the possibility that biopsies from different patient groups can be examined and categorized on the basis of the presence of crypt cell lesions. Until such classifications are possible it is better to consider tropical sprue not as a single disease entity but as a syndrome which is the manifestation of persistent damage to enterocyte and colonic crypt structure and function which results in malabsorption.

The future

Southern Indian tropical sprue, endemic and epidemic, with persistent crypt enterocyte damage and a spread of structural and functional defects in the stomach, small intestine and colon, provides a unique model for aetiological and functional studies. A major priority is to find the aetiology and decide whether primary malabsorption in different tropical regions is the same or different diseases. Understanding the nature of the crypt enterocyte lesion and its prevalence in different groups of patients is cardinal to this. Tropical enteropathy is the background on which tropical sprue develops in indigenous populations. Transregional studies of the adaptation of the gut to tropical sprue in South India. Gut, 26, 710-717. Movement of water and electrolytes. Gut, 26, 17-22. Pathogenesis of tropical sprue depends on understanding the dynamic balance at the epithelioluminal interface of the gastrointestinal tract, which permits the microbial flora and other contents of the lumen to coexist with the delicate single-layered gastrointestinal epithelium.

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