TROPICAL SPRUE: A REVIEW (PART-I)

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Historical Background

Charaka’s description, almost 3000 years ago, of the disease which has now come to be known as tropical sprue stands out as the first and the classical description of the entity. The first description in the English medical literature was made in the West Indies by Hillary in 1759, while the first report in India was in 1818. Large outbreaks of sprue also affected British and Indian troops in India and Burma during World War II. The disorder appeared to be particularly common in hill stations.

The term ‘Tropical Sprue’ came into being only in 1880 when Manson anglicized the Dutch term “Indische sprouw” to sprue referring to the disorder affecting Europeans in China. Baker was the first to recognize in 1957 that intestinal malabsorption due to tropical sprue was not confined to European or American expatriates living in the tropics, but rather was widespread among the indigenous population of South India. Tropical sprue has also been subsequently recognized in other parts of India.

Definition

The original definition of tropical sprue has now been considerably modified because of better understanding of its pathogenesis. Megaloblastic anaemia considered to be essential for the diagnosis is later shown to be a late feature of the disease. The present accepted definition for tropical sprue is “A syndrome among persons in the tropics who have morphologic abnormalities of the small intestine associated with malabsorption of two or more unrelated substances for which no etiology can be ascertained.” This definition, however, has drawbacks. The basis for accepting malabsorption of two substances and not three or one as a diagnostic criterion is not clear. The proposed criteria can be seen in asymptomatic people in tropical countries. The definition therefore needs to be modified in the future taking into consideration the following points. Most people with sprue have gastrointestinal symptoms, the intestinal abnormalities getting relentlessly worse until specific therapy is instituted. Sprue usually results in nutritional deficiencies while in subclinical malabsorption, patients may be asymptomatic, nutritional deficiencies are not seen and intestinal abnormalities revert to normal on moving to a temperate zone. The response of the intestinal abnormalities to specific therapy with folic acid and/or tetracycline is unpredictable in sprue, but not in subclinical malabsorption. These differences however are not so clear cut as suggested—in fact, tropical sprue may be mild and without nutritional deficiencies. Tropical sprue and subclinical malabsorption therefore appear to be a part of a spectrum of related diseases rather than two separate entities.

Various terms used synonymously with tropical sprue include “Dietetic deficieney syndrome”, “Idiopathic tropical steatorrhea” and “Tropical malabsorption.” “Tropical malabsorption” encompasses both tropical sprue and subclinical malabsorption referred to earlier and post-infective malabsorption which follows gastrointestinal infections. Since post-infective malabsorption can be seen following practically any gastrointestinal infections and is of short duration, classifying this condition under tropical malabsorption would lead to unnecessary confusion and the term tropical malabsorption should be best avoided.

The other terms requiring clarification are “Acute tropical sprue” and “Chronic tropical sprue.” “Acute tropical sprue” is a disease seen in expatriates visiting endemic areas and is characterized by a rapid onset of diarrhoea leading to malabsorption, though these features are seen in epidemics too in indigenous subjects. “Chronic tropical sprue” is usually seen in indigenous subjects and the onset of intestinal malabsorption is less dramatic.

Geographical Distribution

Tropical sprue is endemic in India, Puerto Rico and Cuba. It occurs in South America and possibly in Mexico. Tropical sprue has been reported from the Middle East and possibly from Israel. Contrary to what was believed earlier, tropical sprue does occur in Africa.

In India, tropical sprue existing in an epidemic form has been reported in South India while sporadic cases have been reported from many other parts of the country. The cases being seen in North India often being of a milder form. If the disease has not been reported from other parts of India it is probably only due to lack of awareness of the disease and adequate laboratory facilities.

Etiology of Tropical Sprue (Figure 1)

There is still considerable controversy about the etiology of tropical sprue. While much of the available evidence suggests that sprue is an infectious disease, with persistent contamination of the small bowel by enteric pathogens there is evidence that cannot easily be refuted suggesting that nutritional factors may play a predominant role. An additional problem is that investigators have tried to draw a clear line between tropical sprue and subclinical malabsorption which is often difficult. The etiological factors are infection and poor nutrition and in many cases is a combination of the two.

Infection

There are certain strong pointers in favour of tropical sprue being caused by an infectious agent. The disorder
in expatriates is usually a sequel to an initial episode of acute diarrhea; acute enteritis is also known to be followed by malabsorption. Seasonal epidemics of diarrhea are often followed by the development of malabsorption; household epidemics also occur. However, in spite of extensive research no single pathogen has been implicated and in many instances no agents have been isolated from the jejunum of patients with tropical sprue. A study of two different epidemics in similar communities suggested that there could be at least two different etiological agents. An infectious etiology in these epidemics was considered since neither food nor dietary deficiency could be implicated. The occurrence in epidemics, the pattern of spread of the disease with clustering in certain areas and apparent slow spread to other areas of the village and the presence of fever in 25% of these cases all suggest an infectious etiology.

The various etiological agents and the evidences in favour of their being the etiological agent are discussed below.

(i) Bacteria: Tropical sprue occurs where gastrointestinal infections are common. An analogy has often been drawn between tropical sprue and the blind loop syndrome. Both cause malabsorption of vitamin B12 and both respond favourably to antibiotics. The speed and degree of improvement in vitamin B12 absorption suggests an alteration in bacterial metabolism rather than a change in ileal morphology to be important in tropical sprue.

The bacteria that have been isolated from the jejunum in patients with tropical sprue have been limited to the enterobacteriaceae (Klebsiella pneumoniae, Escherichia coli and Enterobacter cloacae) in most cases and anaerobes. The enterobacteriaceae are present in higher numbers in the jejunal mucosa than in the luminal fluid. In some cases Bacteroides ovatus and S. faecalis have been isolated. In normal controls either no organisms or coliform bacteria have been isolated. It is apparent that the organisms isolated from cases of tropical sprue may be causative in that the bacteria isolated have been restricted to the few mentioned earlier and are not seen in normal controls; the jejunal contamination with these organisms even after the subjects are removed from the tropical environment. The presence of coliform organisms in normal controls is explained by the presence of malnutrition in them which may have significant effects on bacterial colonisation. The absence of significantly increased flora in the jejunum of some cases of tropical sprue has been attributed to improper timing of the microbical study.

The bacteria present in the jejunum resist removal from the gastrointestinal tract by adhering to the jejunal cells as has been shown in tissue culture of jejunal cells of patients with tropical sprue. Severe protein calorie malnutrition diminishes the local immune response and facilitates bacterial overgrowth. Delayed small bowel transit time may also be operative in facilitating bacterial overgrowth.

Most of the coliform bacteria are not invasive and most do not produce toxins. Heat-stable and heat-labile toxin producing coliforms have been isolated in cases of tropical sprue but not in patients with the blind loop syndrome. This difference between the coliform organisms in tropical sprue and the blind loop syndrome probably accounts, at least partly, for the different intestinal response in these two disorders to contamination. The bacteria seen in patients with tropical sprue do not produce toxins similar to those produced by strains of E. coli or Klebsiella that are isolated from patients with acute diarrhea. These toxins produce abnormalities in intestinal structure and absorption and have been purified. The intestinal abnormalities in tropical sprue are believed to represent the results of persistent contamination by a single organism while the intestinal changes in subclinical malabsorption result from the residual effect of repeated episodes of transient colonisation by various enteric pathogens.

Koch’s postulates have not been satisfied in tropical sprue largely because of lack of a suitable animal model. Gnotobiotic rats promise to be good animal models but have not been adequately studied for the development of structural and functional intestinal abnormalities.

(ii) Viruses: Viruses have been known to cause malabsorption. A Corona virus or the so-called "Grahame agent" has been implicated in the etiology of tropical sprue. However, the presence of these viruses in control subjects in South India and in children without diarrhea suggests that these viruses may not be specific for tropical sprue.

(iii) Parasites: Giardiasis can clinically resemble tropical sprue and there are similarly altered jejunal bacterial flora. In fact, the early accounts of hill diarrhea in India may have been due to giardiasis and in China some of the cases of sprue were probably due to strongyloidiasis. The parasites isolated in cases of tropical sprue are only additional or incidental factors and the symptoms attributable to tropical sprue continue inspite of eradication of the parasites.
Nutritional factors

(i) Protein malnutrition: Intestinal malabsorption has been known to occur in children suffering from “kwashiorkor” and “marasmus”59-62. Animal models have added support to the concept that protein malnutrition may be important in the etiology of tropical sprue. A kwashiorkor-like syndrome has been produced in rhesus monkeys maintained for several months on a diet inadequate in proteins. In this model, malabsorption of vitamin B12 and changes of villous atrophy in the jejunum were seen53, 54. This experimental model, however, is not comparable to human tropical sprue as complete depletion of protein is not seen in clinical practice. A principal defect of tropical sprue was therefore produced both by gross and marginally deficient protein diets55. At a 2% level of protein intake the animals became frankly diseased after two months, but at a 5% protein intake the symptoms appeared after five months. The animals lost weight and facial edema appeared. Intestinal absorption of fat, D-xylene, radioactive vitamin B12 and folie acid showed marked depression. The jejunal mucosa showed moderate villous atrophy, histochemical and electron microscopic changes were consistent with those seen in human tropical sprue syndrome. It appears, therefore, that protein malnutrition plays an important role in an experimental sprue like syndrome in monkeys and this animal model is expected to shed light on the etiological factors in tropical sprue56.

(ii) Folic acid, vitamin B12 and other vitamins: The folie acid and vitamin B12 deficiency seen in tropical sprue is most likely a secondary phenomenon as the occurrence of this condition in well-nourished individuals makes a primary role of folate or vitamin B12 unlikely. The folie acid deficiency, however, contributes to impaired jejunal mucosal function57, 58, even though the small bowel changes precede systemic folate deficiency59. A local deficiency of folate may be present in these cases60. Further evidence for the association between malabsorption and folate and vitamin deficiency comes from studies which show the presence of malabsorption in pregnancy and the puerperium associated with a decrease in vitamin B12 and folate stores61.

There is, however, some evidence against folate being causative in tropical sprue. In patients of severe nutritional folate deficiency anemia, absorption of glucose, xylose and glycine is normal despite villous blunting in the jejunal mucosa62. In rats nutritional folate deficiency has not been shown to cause malabsorption. The paradox of normal absorption in the presence of blunting of the villi in folate deficiency needs explanation. This is because the enterocytes acquire digestive enzymes such as disheherdases as they migrate up the villus63. Because the cell transit time from crypt to villus tip is prolonged in folate deficiency, the epithelial cells on the villus are ‘hypertrophy’ and acquire a greater quantity of brush border enzymes. There is, however, an impaired absorption of water and electrolytes64. It must be emphasised that these are animal studies and need not necessarily apply to human subjects.

Folate deficiency predisposes to bacterial overgrowth by affecting lymphocyte function in the lamina propria. Ethanol is one of the metabolic products of the jejunal bacteria in tropical sprue and this can exert a deleterious effect upon intestinal enzymes, an effect which can be reversed, at least partly, by folate65.

(iii) Fats: It has been suggested that excessive consumption of fats can play a role in determining the persistence of bacterial bowel contamination66. The excessively consumed unsaturated fatty acids inhibit the normal predominant gram positive bacteria and permit overgrowth of coliforms. These factors may be contributory in Puerto Rico, but are unlikely to be important in the Indian situation. In tropical sprue there may be depletion of essential fatty acids which, however, does not explain the mucosal accumulations of triglyceride in the jejunal mucosal cells in tropical sprue67.

Immunity

The local T lymphocyte response has been known to lower villus enzyme levels68. Immunological studies performed on patients with tropical sprue have not been useful in clarifying the etiology of the disease69. Cytotoxic T cells have been found to be increased and secretory IgA levels have been found to be low in patients with tropical sprue. The significance of these findings is not clear.

Pathophysiology of Disturbances seen in Tropical Sprue (Figure 1)

(i) Morphological changes: The salivary glands do not seem to be involved in tropical sprue66. The gastric changes include histamine fast achlorhydria, diminished intrinsic factor and histologically atrophic gastritis67. The predominant changes are in the small bowel with maximal involvement of the jejunum68. The presence or absence of steatorrhea usually depends on the site and severity of mucosal lesion69. There is also a correlation between the severity of involvement and the duration of symptoms. Stunting of the villi and columnar cells, a decrease in mucosal thickness and an increase in the villous width and lamina propria infiltrate are seen with progressive increase in duration of symptoms70.

The dissecting microscope appearances of biopsies from patients with tropical sprue are quite variable and may range from normal finger-shaped villi to a completely flat mucosa with a mosaic pattern71. The mucosal height is usually decreased when marked villus abnormalities are present72. Accumulation of fat droplets in jejunal enterocytes have been seen in many patients of tropical sprue73, and is confirmed on electron microscopy74. Ultrastructural studies in addition indicate injury to the brush border system.

The variation in jejunal morphology on light and dissection microscopy may be due to inadequate sampling of the total biopsy piece. A three dimensional reconstruction of jejunal biopsy specimens focuses the limitations of interpretation of the findings of the dissection and light microscopy73. It must also be emphasized that the mucosal changes are not specific and technical factors can cause variation in the morphology studied74.

Enzyme analysis of jejunal biopsy homogenates in tropical sprue show a selective reduction in brush border enzyme with little change in other enterocyte structures76.
(ii) Intestinal malabsorption. (a) Fluid and electrolytes: Normal control subjects are usually in net absorption with respect to water, Na⁺ and Cl⁻. In Indian controls, the net absorption of water and electrolytes is significantly less than that in the English79. There are considerable differences between the acute and chronic forms of tropical sprue with respect to water and electrolyte transport.79-81 In patients with acute tropical sprue there is a net secretory state for water, Na⁺ and Cl⁻. The normalization of these changes after antibiotics suggests that bacterial toxins are possibly involved79-80. In chronic tropical sprue, however, the water and electrolyte changes are indistinguishable in south Indian subjects from their controls81. In the same study group the microflora of the upper intestine were also indistinguishable between the subjects and controls81. Since the water and electrolyte changes in controls and in patients with chronic tropical sprue are not much different, the larger stool volume must be contributed by other factors such as steatorrhea.

(b) Fat absorption: Tropical sprue may occur without steatorrhea; the presence of steatorrhea is no longer considered essential for the diagnosis of tropical sprue. The degree of steatorrhea correlates poorly with stool volume. The steatorrhea is principally due to impaired transport of lipid82-83. Jejunal bile salt concentrations are normal and deconjugation usually does not occur84-85. The presence or absence of steatorrhea depends to some extent on the dietary fat intake as it is seen that very low fat diets can abolish the steatorrhea86.

(c) Vitamin B₁₂ absorption: The malabsorption of vitamin B₁₂ is predominantly due to bacterial metabolism87 and uncommonly due to absent intrinsic factor, seen in 5% of the cases of tropical sprue86. The role of bacteria in vitamin B₁₂ malabsorption has been extensively studied82. Examination of centrifuged ileal contents shows only a small amount of orally administered B₁₂ is present indicating predominant bacterial metabolism of the vitamin B₁₂88. Similar conclusions have been drawn using a modified Schilling test in the same group of patients with labelled vitamin B₁₂ bound to intrinsic factor. Besides metabolising B₁₂, the bacteria may contribute to vitamin B₁₂ malabsorption either by producing a vitamin B₁₂ analogue which is capable of blocking the uptake of vitamin B₁₂ in the diet89 or by causing damage to the ileal receptor for vitamin B₁₂90.

(d) Folate absorption: Dietary folate polyglutamatet require hydrolysis by a small intestinal brush border enzyme before monoglutation absorption can take place. Even though the other brush border enzymes may be low the folate conjugate activity of the jejunal mucosa is high in tropical sprue. This evidence suggests that folate conjugase is an intracellular enzyme and the presence of intraluminal hydrolytic products of labelled polyglutamate is due to a process of back diffusion after transport of intact polyglutamate into the cells90. Perfusion studies with radiolabelled folate in patients with tropical sprue have showed impaired hydrolysis of polyglutamate and impaired absorption of its digestive product-folic acid, although levels of total conjugate are apparently normal90. Jejunal crypt cells have higher synthetic rates of DNA and normally need the folate derived enzyme thymidylate synthetase; however, in folate deficiency, preformed thymidylate may be utilised. This mechanism is used in tropical sprue91.

Malabsorption of folate in tropical sprue can occur either due to impaired uptake of folate from purified monoglutamates and polyglutamates or due to inability to process dietary folates. The possibility of folate binding proteins in the diet of patients with tropical sprue needs further study. In addition, in patients with tropical sprue, secondary folate deficiency produced, compromises the gastrointestinal mucosal function and may precipitate a relapse.

(c) Carbohydrate malabsorption: Malabsorption of glucose and galactose occurs due to changes in the small intestinal mucosal cell. Lactose intolerance also commonly seen in tropical sprue is due to secondary lactase deficiency92-93. D-xylene absorption measurement is a standard test of jejunal mucosal integrity and is often impaired in tropical sprue94.

(f) Amino acids: Malabsorption of the amino acids methionine, leucine, valine95 as well as the dipeptide glycyl-glycine96 have been shown. Besides malabsorption, excessive loss of protein into the intestinal tract occurs96. Reduced hepatic synthesis of albumin also contributes to the hypoalbuninemia97.

(g) Other nutrients: The absorption of iron has not been adequately evaluated. Lowered absorption of calcium, magnesium and vitamin-D are seen, these defects being corrected by administration of folate. Pyridoxine absorption is usually normal while that of vitamin A is impaired98. The impaired absorption of vitamin A and D is secondary to fat malabsorption. The hypomagnesaemia is secondary to hypocalcaemia which in turn is due to vitamin D deficiency. Recently, it has been suggested that vitamin D and its metabolites may have an effect on the virus size and migration rate94.

(iii) Nutritional deficiencies and weight loss

The extent to which tropical sprue could have a bearing on the health of a community is not clear. Large number are affected in developing countries99, the incidence being underestimated because of lack of recognition of the disease. It has been estimated that 200-300 K cal/day100 or roughly 10% of the daily calorie intake are lost in the stool of patients with tropical sprue. In areas where a large number of severe cases of tropical sprue are seen, the disease is the cause of malnutrition in almost 50% of the population101 and in villages in Guatemala the fecal energy loss even in asymptomatic patients is more than four times that in Western subjects102.

Weight loss in tropical sprue occurs due to reduced dietary intake resulting from anorexia caused by vitamin deficiency103 and is perhaps the same as in celiac sprue.

The majority of patients with tropical sprue are iron deficient104, megaloblastic anemia due to folic acid deficiency is common105,106. In our series vitamin B₁₂ levels were abnormal in 30% of cases, while serum folic acid levels were low in 62% of cases. Both vitamin B₁₂ and folic acid levels were low in 27.2% of our cases.
The bone marrow was normoblastic in 80% of our patients. Tropical sprue may on occasions give rise to secondary pellagra. There may, in addition, be a decreased urinary excretion of amino acids, hypoalbuminemia and decreased urinary excretion of steroid metabolites. Figure 1 gives a unified concept of the etiopathogenesis of tropical sprue, with relation to the nutritional and infectious etiology of tropical sprue. The pathophysiology of the disturbances seen are also given.

(To be concluded)