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104 Tropical Sprue: Enteropathy

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SHORT VIEW SUMMARY

Definition
- Syndrome of diarrhea, malabsorption of at least two distinct nutrients, abnormal duodenal histopathology, and weight loss.

Epidemiology
- Most frequent in Asia and the Caribbean islands, more frequent in adults than children; occurs in long-term travelers to endemic regions.

Microbiology
- No single agent associated with causality, small bowel overgrowth common.

Diagnosis
- Appropriate clinical syndrome (persistent diarrhea, malabsorption of at least two distinct nutrients, weight loss) with consistent small bowel series or upper endoscopy. Response to folate and tetracycline ultimately confirms diagnosis.

Therapy
- Removal from area of risk, treatment with folate and tetracycline.

Prevention
- Good hygiene practices.

Tropical sprue, also called *postinfectious tropical malabsorption,* is a syndrome of enigmatic origin that is characterized by a prolonged diarrheal illness and malabsorption of two or more substances in persons in the tropics who have no other obvious reason for malabsorption. Tropical sprue has been recognized since the second or third century AD, when Aretaeus of Cappadocia reported on "The Coeliac Affection" and in India in the Charaka Samhita.[1] The first mention of sprue in the modern medical literature was in 1747, when Hillary emigrated from England to Barbados and published his observations on a prolonged tropical diarrheal disease in native islanders. The English term *sprue* is an adaptation from the Dutch *sprouw,* which was originally used to refer to persistent diarrheal disease in Holland (probably celiac disease). The term *sprue* first was used in 1880 by Manson for the persistent wasting diarrhea that occurred in tropical countries.[2] Knowledge about the cause or pathogenesis of sprue did not advance significantly until investigations were begun after recognized outbreaks during World War II. The distinction between celiac sprue and tropical sprue was not clear until the early 1970s.

EPIDEMIOLOGY

Although sprue is considered a disease of tropical locales, there are distinct geographic areas of risk within the tropics. Tropical sprue has been identified most readily in Asia and the Caribbean islands, and there are isolated areas of particular risk within both hemispheres. Sprue is relatively common in the indigenous populations of Puerto Rico, Haiti, the Dominican Republic, and Cuba, but it is not seen in the rest of the Caribbean islands and is no longer recognized in Barbados.[3,4] It is seen in northern South America, Venezuela, and Colombia but rarely in Central America or Mexico. It is less common than previously but remains on the Indian subcontinent, from the Himalayas to the south, and it has been recognized in Myanmar and the Philippines.[5-7] Infrequent cases of tropical sprue were documented in Africa until the 1970s; cases have been recognized in Rhodesia (now Zimbabwe) and South Africa, and tropical sprue has developed in expatriates living in Nigeria.[8] There may be endemic foci of tropical sprue in the Middle East as well, with a spruelike illness recognized in Turkey.

In contrast to other endemic diarrheal illnesses in the tropical world, tropical sprue is a disease mainly of adults. Children are thought to be relatively spared, although disease has been documented in all age groups. Very young children have not been found to have tropical sprue; this may represent a beneficial effect of breast-feeding. In studies of family outbreaks of tropical sprue in South India, even older children developed disease at a significantly lower rate than adults.[9] The reason for this is not clear. Persistent diarrhea develops in children more commonly in parts of the world where the environment is contaminated more heavily with potentially disease-causing microorganisms.[10] Tropical sprue may be one of the causes of prolonged diarrhea and wasting in this age group as well, but studies such as small bowel intubation and cultures or biopsy have shown conflicting results regarding the correlation of small bowel colonization with persistent diarrhea.

Some patterns of disease expression are of particular interest in tropical sprue. There are clear epidemics of the disease, which have been documented best in families and villages in South India.[9] There have been descriptions of sprue houses, in which successive tenants have developed disease, and an outbreak was described in which more than half of the exposed persons in an isolated extended family developed tropical sprue within 3 months of onset of disease in the index case. Well-documented outbreaks of sprue affecting entire villages have also been reported, mostly from the Indian subcontinent. Such an epidemic pattern suggests an underlying infectious cause.

There has been seasonal variation in outbreaks of tropical sprue as well. An increased rate of mild tropical sprue in the setting of an increased rate of diarrheal disease was seen more often from March to July than at other times of the year for at least 4 years at an American military base in the Philippines.[7] In these outbreaks, sprue occurred in American military personnel and their dependents, who were eating a high-calorie, Western-style diet. A seasonal variation also has been documented in the rate of occurrence of tropical sprue in the indigenous population of Puerto Rico.[4] This seasonal variation also lends credence to the possibility of an underlying infectious cause.

As suggested by the outbreaks in American military personnel, tropical sprue occurs in expatriates living in endemic areas. Tropical sprue was originally recognized in expatriates and British colonists in India in the early 19th century and subsequently in the Dutch in Java, the French in Indochina, and Americans in the Philippines, Vietnam, and Puerto Rico. Tropical sprue or malabsorption with jejunitis (tropical enteropathy) has been described in Peace Corps volunteers and has occurred sporadically in travelers.[11] Generally, tropical sprue develops in an expatriate who has lived for a prolonged time (6 months to 1 year) in an endemic area. Rare cases also have been described in short-term travelers. Tropical sprue is also recognized in immigrants who leave endemic areas, although they may not complain of gastrointestinal symptoms until they have been out of the endemic area for a prolonged period.[12] These exposure data also suggest an infectious origin for tropical sprue.

Recent studies have suggested that sprue occurs far less frequently than it did previously. Sprue was a less common cause of malabsorption in adults in Delhi than celiac disease in 2011 but remained the most common cause of malabsorption in South India in 2011.[13,14] Anecdotally, clinicians continue to report the occurrence of cases in endemic areas.

KEYWORDS

bacterial overgrowth; diarrhea; hygiene; long-chain fatty acids; macrocytic anemia; malabsorption; persistent diarrhea; small bowel colonization; tropical enteropathy; villus atrophy

CAUSES

There is a strong presumption that tropical sprue is caused by an enteric infection, perhaps in individuals predisposed by some nutritional deficiency. The facts lending support to this theory include the following: (1) often, the prolonged episode of tropical sprue is initiated by an episode of acute diarrheal disease; (2) there is an epidemic and seasonal nature to the epidemiology of the disease, as noted; and (3) the disease responds most often to treatment with antibiotics with or without nutritional supplements. The precise nature of the infection that leads to development of tropical sprue is less clear.

Multiple studies in Asia and the Caribbean islands have shown small bowel bacterial overgrowth in patients with tropical sprue.[11,15,16] Although some bacteria normally live in the upper small bowel of healthy persons, the organisms isolated from this region of the gut in healthy asymptomatic individuals are most often gram-positive. Streptococci, staphylococci, and lactobacilli are among the common isolates, and these are present in small numbers. In the distal small bowel, the cecum, and the colon, anaerobes and facultative gram-negative organisms predominate in normal persons. Small bowel cultures from travelers with tropical sprue show increased numbers of gram-negative rods, including *Alcaligenes, Enterobacter aerogenes,* and *Hafnia* spp. In small bowel cultures from persons with tropical sprue who were native to India, Haiti, or Puerto Rico, *Klebsiella, Escherichia coli,* and *Enterobacter cloacae* were the most common organisms. Carefully done studies in South Africa and India documented similar organisms in similar concentrations in the small bowel of asymptomatic control patients and in patients with tropical sprue, suggesting that environmental contamination may predispose to increased small bowel flora.[11,15,16] In another series of patients from India, the number of organisms found in the small bowel of tropical sprue patients was the same as that found in the small bowel of healthy controls, but the type of organisms isolated varied.[15] Other organisms, especially *Enterobacter* and *Veillonella,* were isolated more frequently from the small bowel of patients with tropical sprue than from healthy controls.[17] Demonstration of organisms does not prove cause and effect, however.

Gram-negative organisms isolated from the small bowel of tropical sprue patients in Haiti were found to have a secretory effect, presumably by toxin production, in rabbit ileal loops and rat perfusion studies. These supposedly enterotoxigenic organisms have not been studied for the presence of any of the recognized secretory toxins by currently available methods, such as DNA probes or enzyme-linked immunosorbent assay (ELISA), nor have they been studied for the presence of colonizing factors, such as pili or the hydrophobic surface proteins that are found in many enteric pathogens. *E. coli* and *Klebsiella* isolated from Indian patients with tropical sprue were not found to produce heat-stable or heat-labile enterotoxins when tested.[18] Some animal studies have suggested that small bowel overgrowth by colonizing nontoxigenic *E. coli* can produce a secretory diarrheal syndrome if the level of colonization reaches a high enough concentration within the small bowel.

Other studies have further suggested that enteroaggregative *E. coli* are associated with malnutrition, with or without persistent diarrhea, and with intestinal inflammation and cytokine production.[19] In addition to its association with persistent diarrhea in children in tropical developing areas, enteroaggregative *E. coli* in patients with acquired immunodeficiency syndrome (AIDS) is associated with persistent diarrhea that improves with antimicrobial therapy.[20,21] Strains of *E. coli* from patients with tropical sprue have not been examined for adherence factors. The presence of bacteria in the small bowel may potentiate the symptoms caused by the small bowel parasite *Giardia lamblia,* and the interaction of small bowel bacteria and parasites has been considered as a possible cause of tropical sprue.[22] Infection with hookworm or *Strongyloides stercoralis* has also been discussed as a possible cause for tropical sprue. Reports of tropical sprue occurring in the presence of orthomyxovirus or coronavirus particles in the stool have also appeared in the literature. Cases of tropical sprue have been reported after an intestinal infection with fungus or the blue-green algae *Prototheca.* Although the traditional definition of tropical sprue excludes patients with diarrhea on the basis of recognized pathogens, it is possible that improvements in diagnostic techniques would permit the identification of organisms that are or have been associated with tropical sprue but previously were not able to be isolated or identified. Whether tropical sprue is distinct from tropical or environmental enteropathy has never been clear; these syndromes may exist at the ends of the spectrum of a single disease, with sprue being the more advanced and symptomatic form of the more frequently asymptomatic environmental enteropathy.[1] Sequence-based microbial identification is an example of a significantly more sensitive technique that may be beneficial in elucidating intestinal microbiota as it contributes to the pathogenesis of tropical sprue and may clarify the relationship to environmental enteropathy.[1,23]

The fact that small bowel overgrowth, as it occurs spontaneously in a certain segment of the population in resource-limited countries or after an acute enteric infection, may precipitate a series of intestinal insults that proceed to full-blown tropical sprue in susceptible persons is at present the most likely explanation for the cause of tropical sprue. The predisposition for progression from intestinal insult to tropical sprue is less easy to explain. Malnutrition, whether generalized or presenting as specific micronutrient deficiencies, may be a predisposing factor, but is neither necessary nor sufficient, as shown by the occurrence of tropical sprue in apparently well-nourished military personnel and their dependents. Small bowel overgrowth may alter intestinal transit time and promote further overgrowth and intestinal stasis, but it cannot explain the initial colonization that induces the episode.

In vitro data suggest that small bowel colonization by *E. coli* may be increased by low levels of cytokines, as might be expected in chronic parasitic infections in the developing world. As noted, certain organisms, such as enteroaggregative *E. coli,* can alter the intestinal environment by the induction of intestinal proinflammatory cytokines and intestinal inflammation.[24] There has been no genetic predisposition noted for tropical sprue as there has been for celiac sprue, and the inflammatory cytokine profile in the lymphocytes of the small bowel in patients with tropical sprue has not been described.

The processes that control the normal colonization of the small bowel are not well understood; the forces that may disrupt these normal processes to permit abnormal colonization are even less well understood. Some factors that can affect the normal small bowel colonization process include gastric acidity, which controls the entry of viable organisms into the small bowel, and intestinal mucin glycoprotein, which contains receptors for, and specifically binds, a variety of bacteria within the small bowel lumen.[25]

Bacterial binding to mucin is presumed to promote clearance of pathogenic organisms to protect the small bowel, but it may promote colonization by nonpathogenic organisms or promote small bowel colonization by pathogens when the mucin is damaged by malnutrition, an inflammatory process, or bacterial proteases or mucinases. Some loss of the protective mucin layer in tropical sprue is suggested by evidence that the bacteria visualized are often associated tightly within the mucosa rather than being free within the lumen of the gut.[2] Damage to the protective mucin layer may also permit epithelial cell damage by other small bowel antigens. The presence of free bile acids within the upper small bowel can alter intestinal bacterial growth rates and colonization, but bile acid concentrations have not been abnormal in patients with tropical sprue, and the bacterial organisms that have been cultured from patients with tropical sprue are not organisms that typically alter bile salt metabolism.[18]

Intestinal immunologic dysfunction has been suggested as a factor that might predispose to abnormal bacterial colonization in tropical sprue. Patients with deficiencies of secretory immumoglobulin A (IgA) are subject to more frequent and severe bouts of enteric infections. In addition to secretory IgA, lymphoid tissue is present throughout the small bowel focally in Peyer patches and diffusely as mucosal lymphocytes. When small bowel lymphocytes were characterized in patients with tropical sprue and in control patients with irritable bowel syndrome in southern India, there was no difference in the number of IgA-producing, IgG-producing, or IgM-producing lymphocytes between the two groups.[26,27] Patients with sprue had increased numbers of lymphocytes in the crypt epithelium, with a higher percentage of immunoblasts and a higher mitotic index.[28] These data can be interpreted as evidence that lymphoid activation does occur in tropical sprue, but that it is probably secondary to whatever primary process institutes the disease, rather than being an inciting process itself.

It has also been postulated that dietary fat might play a role in tropical sprue. Similar to the permissive effect of protein ingestion in the pathogenesis of pig-bel, the intake of long-chain fatty acids has been studied as a potential causative factor for tropical sprue.[29] The seasonal epidemic occurrence of tropical sprue in Puerto Rico immediately follows a traditional holiday feast of pork, which is rich in long-chain fatty acids.[30] There are several mechanisms whereby these long-chain fatty acids might contribute to the production of clinical tropical sprue. Long-chain fatty acids can alter intestinal motility and delay intestinal transit time. Plasma levels of enteroglucagon and motilin are increased significantly in patients with tropical sprue; motilin slows gastric emptying, and enteroglucagon slows intestinal transit.[31] Recent studies have also demonstrated abnormalities in PYY and neurotensin after infusion of fat in some patients with sprue, which may contribute to altered motility and bacterial overgrowth.[32] Intubation studies have shown that intestinal infusions of fat increase plasma enteroglucagon levels and decrease intestinal motor activity. Fat within the gut lumen also inhibits the mucosal sodium-potassium fluxes and the magnesium adenosine triphosphatases, which can contribute to malabsorption of water and electrolytes in the intestine and raise the pH of the mucosal microenvironment.[29,33]

The elevated mucosal pH produced by intestinal fats also has been associated with increased growth of gram-negative bacteria in the lumen of the small bowel, and a switch to a high-fat diet has been associated with alterations in the intestinal microbiota.[34,35]

The elevation of mucosal pH and the presence of fatty acids within the lumen of the gut also may impair the ability of the intestine to absorb folate; folate deficiency may potentiate the intestinal dysfunction that precedes it.[36] Folate deficiency leads to a decreased number of gut epithelial cells, as assessed by DNA concentrations, and to villus atrophy. Additional structural alterations are seen in the intestine with folate deficiency, including crypt hypertrophy, villus blunting, and megaloblastic changes in the epithelial cells. These changes are nonspecific and are similar to those seen with vitamin B_{12} deficiency, celiac disease, or tropical sprue. Functionally, the folate-deficient gut is less efficient in absorbing water, electrolytes, and carbohydrates than the normal small bowel.[37] It is likely that whatever the initial insult to the gut may be in tropical sprue, the resulting folate malabsorption and deficiency contribute to the further pathogenesis of disease (Fig. 104-1).

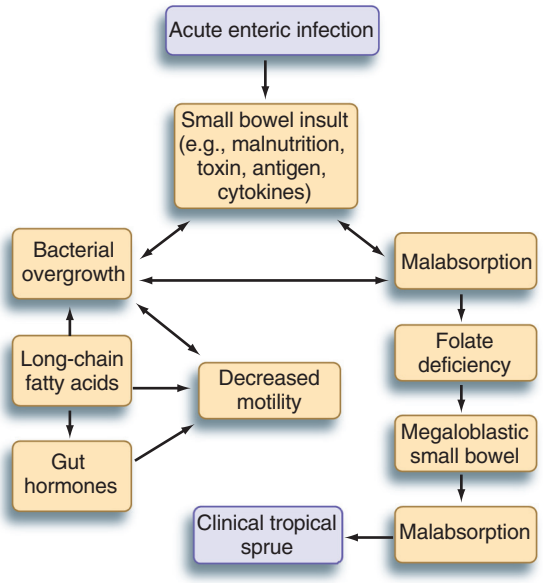

FIGURE 104-1 Proposed pathogenesis of tropical sprue. The complex vicious cycle of small bowel insult that results in bacterial overgrowth and malabsorption, as well as further small bowel damage by luminal long-chain fatty acids and dysregulation of intestinal hormones, may promote disease in susceptible persons after an acute enteric infection.

Exocrine pancreatic insufficiency has been documented in patients with tropical sprue by the indirect pancreolauryl test. The pancreolauryl test was abnormally low in patients with tropical sprue and was correlated with damage seen on intestinal biopsy.[38] Pancreatic function improved with therapy in this study.

CLINICAL MANIFESTATIONS

The classic clinical features of tropical sprue are nonspecific and simply reflect the symptoms of malabsorption. Changes in hygiene, increased access to medical care, and/or improved access to water supplies may all be altering the frequency and severity of malabsorption. Currently, the diagnosis is made when the presentation is still quite subtle compared with the severe disease that was the more common presentation in the past. Malabsorptive symptoms include prolonged diarrhea, abdominal cramping, and anorexia, with or without nausea and secondary weight loss. Other associated, but less common symptoms, also related to the malabsorption of specific nutrients and subsequent malnutrition or micronutrient deficiencies may include peripheral edema, glossitis, stomatitis, and dermatitis.[34,38] Fever may occur at the onset of sprue-related diarrhea (especially in Asia). Although the presence of fever has been suggested as a means to distinguish Caribbean from Asian sprue, this distinction has not been observed consistently. Fever rarely persists for the course of disease, which may span months to years. Signs and symptoms related to anemia may also occur; pallor and weakness are most common early in disease. Later in the course of tropical sprue, peripheral neuropathy, confusion, and, if the anemia is severe enough, congestive symptoms reflecting high-output failure may occur.

Many patients can pinpoint the onset of disease; tropical sprue rarely has an insidious onset and far more often is associated with an obvious acute episode of diarrhea that then becomes prolonged. Patients with tropical sprue may recall other people with similar acute illnesses or being exposed to someone with an acute illness just before getting sick themselves. Because the operative definition of tropical sprue implies that the function of the gut was normal before the development of the disease, ideally the alteration of bowel habits from a normal pattern by the inciting episode of acute diarrheal disease should be notable. In practice, especially in the resource-limited world, the distinction between normal and abnormal bowel habits may not be so clear.

Patients describe crampy abdominal pain, multiple soft or loose stools daily often with mucus, and exacerbation of symptoms with food consumption. Patients may also complain of nausea and bloating that lead to decreased appetite and decreased oral intake. The precise presentation of a patient with tropical sprue depends on the duration of illness and the extent of malabsorption.

Malabsorption of specific nutrients may lead to other symptoms and syndromes.[39] Lactose intolerance often develops early in the course of tropical sprue. The anemia of tropical sprue is most often macrocytic and related to vitamin B_{12} and folate malabsorption. Iron deficiency may also occur, related to malabsorption, and may turn a macrocytic anemia into a normocytic anemia. Impaired absorption of calcium, vitamin D, and magnesium may occur, with resulting osteopenia.[40] Patients with tropical sprue also have malabsorption of fats and, depending on the severity of fat malabsorption, may complain of bulky, floating, or foul-smelling stools.

Spontaneous recovery may occur, but this is not inevitable. Spontaneous recovery is more common in travelers to areas endemic for tropical sprue who return to their native environments. Patients who have emigrated from endemic areas and patients living in endemic areas often require medical therapy to alleviate symptoms. Because the clinical manifestations of tropical sprue are nonspecific, symptomatic response to specific therapy can be considered additional evidence that the patient had tropical sprue.

INTESTINAL ABNORMALITIES

Although the secretory and malabsorptive syndrome seen in tropical sprue suggests preferential damage to the small bowel, functional abnormalities are seen in the large bowel as well. Functional changes in the small bowel mirror the morphologic changes seen and are most prominent in the ileum and jejunum. In tropical sprue, the jejunum is

in a net secretory state, with active secretion of water, sodium, and chloride[41]; however, glucose-linked absorption remains intact, as it does for many other secretory infectious diarrheal syndromes.[42] In tropical sprue, there is malabsorption of bile acids and vitamin B_{12} in the ileum. Bile acid malabsorption leads to fat malabsorption and malabsorption of the fat-soluble vitamins D, A, K, and E. Brush border enzymes are decreased functionally and are less efficient in digesting and absorbing disaccharides, such as lactose.[43,44] Xylose, glucose, and folate malabsorption occur, as does malabsorption of minerals such as calcium and magnesium. Amino acid malabsorption occurs; protein metabolism is complicated further by loss of albumin in the lumen of the damaged small bowel.[45]

Most of the functional changes in tropical sprue may be related to small bowel mucosal damage represented by the morphologic changes seen, but the hormonal regulation of the gut is also dysfunctional in this disease.[46] Postprandial insulin and gastric inhibitory peptide are reduced in tropical sprue; enteroglucagon and motilin levels are increased. In chronic tropical sprue, gastric acid secretion and secretion of intrinsic factor may also be affected. Transit time through the small bowel is slowed, as measured by breath hydrogen testing.[47-49]

In the few studies of colonic function in tropical sprue that have been done, the ability of the colon to absorb water is decreased in patients compared with controls. There is speculation that the dysfunction of colonic cells may be related to damage by excess fatty acids in the gut lumen or bacterial toxins or infection. Although there is physiologic confirmation of the ability of fatty acids to disturb the absorptive function of colonocytes and small bowel enterocytes, data suggesting that colonic infections are important in the pathogenesis of tropical sprue are lacking.

HISTOPATHOLOGY

Partial villus atrophy is the hallmark histologic change seen in the small bowel in tropical sprue, as opposed to the flattened mucosa that is characteristic of celiac sprue.[50] The villi in tropical sprue progressively shorten and thicken, forming fused leaves after about 4 months of illness. These histologic changes are seen in the jejunum and the ileum, where the changes in absorption also are localized. These histologic changes are not specific for tropical sprue but may be present in severe folate deficiency or with bacterial overgrowth. In distinction, in celiac disease, blunting of villi and crypt hyperplasia is seen and lymphocytes are noted to infiltrate the crypts.

Microscopically, the mucosa is thin, with an infiltrate of chronic inflammatory cells consisting of plasma cells, histiocytes, lymphocytes, and eosinophils. As noted, these lymphocytes have been characterized, and IgA, IgG, and IgM lymphocytes are present in numbers equal to those of asymptomatic control patients.[27,28] An increased mitotic index can be seen in the crypt cells; the nuclei of the crypt cells may also appear megaloblastic.[45,51] An increased number of goblet cells may be present, and lipoid vacuoles have been seen within the basement membrane. To date, there is no convincing evidence that tropical sprue is an immunologically mediated disease.

DIAGNOSIS

Because the symptom complex of tropical sprue is nonspecific, the travel and exposure history of the patient are crucial in making the diagnosis. Tropical sprue should be considered in a patient who presents with chronic diarrhea, weight loss, and evidence of malabsorption. Attempts should be made to ascertain the onset of the diarrheal illness, duration of diarrheal illness, degree of weight loss, frequency and character of the stool, and any other systemic complaints, such as prolonged fever, jaundice, or itching, that might suggest alternative explanations for the diarrheal illness. Information regarding travel to, residence in, or emigration from the tropics should be requested. Although there have been sporadic case reports of mild spruelike illnesses occurring after diarrheal illnesses in temperate climates, this so-called temperate sprue is rare and a history of exposure to an endemic area should be present to entertain the diagnosis of tropical sprue.[30]

Pertinent medical history should also be obtained, with particular emphasis on any surgical procedures that might have altered the anatomy of the bowel, predisposing to a blind loop syndrome, or any medications that could predispose to small bowel overgrowth. Social history, in addition to travel and exposures, should include questions relating to possible human immunodeficiency virus (HIV) exposure because HIV infection is a major risk factor for the development of chronic diarrhea.[52] History pertaining to symptoms of specific nutrient deficiencies, such as night blindness secondary to malabsorption of vitamin A, would be expected only in prolonged disease.

There are no diagnostic physical findings for tropical sprue. The physical examination should document presence or absence of fever, volume status by any orthostatic changes, body weight, evidence of weight loss such as temporal wasting, and presence or absence of significant lymphadenopathy or abdominal masses. Hyperactive bowel sounds may be the only pertinent abdominal finding. Signs of anemia, such as pallor, are notoriously nonspecific but can be sought. Signs of specific nutrient deficiencies may also be present on physical examination: Cheilosis, stomatitis, glossitis, rashes, dermatitis, koilonychia, muscle pain or weakness, peripheral neuropathy, or edema can suggest deficiencies of iron, zinc, vitamin B_{12}, folate, vitamins D and E, or protein. Deficiencies of any of these nutrients could be present in tropical sprue because of malabsorption by the damaged small bowel.

Laboratory evaluation of a patient with suspected tropical sprue can be minimal or extensive, depending on the degree of suspicion and the urgency for diagnosis. A simple, complete blood count showing a macrocytic anemia in a high-risk patient in the appropriate clinical setting could be sufficient to proceed with other, more confirmatory diagnostic tests, such as a small bowel biopsy. A more complete laboratory evaluation includes serum vitamin B_{12} and red blood cell folate levels, serum carotene concentration, or, preferably, a 72-hour fecal fat determination. Stool examination to exclude *Giardia* is useful; stool culture looking for bacterial pathogens is less likely to be helpful in chronic diarrhea.

Ultimately, a small bowel series with small bowel follow-through showing flattened mucosal folds, luminal dilation, or flocculation of the barium meal can suggest tropical sprue.[52] An upper endoscopy with duodenal aspirate for parasites and biopsy can be diagnostic of tropical sprue in the appropriate clinical setting. Enhanced magnification endoscopy (EME) has been shown to be more sensitive in detecting villus atrophy than standard endoscopy and may assist in making a noninvasive diagnosis of sprue. In a study of 15 patients diagnosed with sprue by intestinal biopsy in Caracas, Venezuela, atrophy was demonstrated in 93% of patients by EME, whereas standard endoscopy was able to detect atrophy in only 20% of patients.[53] Documentation of abnormal transit time by small bowel follow-through or breath hydrogen testing, which also can imply bacterial overgrowth, suggests but is not diagnostic of tropical sprue. The differential diagnosis that must be considered in a patient with chronic diarrhea, weight loss, and malabsorption, even in a clinical setting consistent with tropical sprue, should include giardiasis, cryptosporidiosis, coccidiosis *(Cystoisospora belli),* capillariasis, strongyloidiasis, celiac sprue (gluten enteropathy), lymphoma, intestinal tuberculosis, blind loop syndrome, pancreatic tumors, Whipple's disease, and microsporidia-associated HIV enteropathy. If diagnosis remains obscure, biopsy is considered to be very sensitive and will allow the syndromes to be clearly differentiated. Celiac disease, or gluten enteropathy, can be more definitively diagnosed by sending antigliadin or antiendomysial antibodies.

THERAPY

Treatment with folate alone improves the symptoms of tropical sprue but does not cure the diarrhea. Combination therapy with tetracycline and folate seems to be most effective in symptom resolution and cure of diarrhea with promotion of weight gain.[54,55] Treatment with 250 mg of tetracycline four times daily and 5 mg of folate daily for 1 month has been effective for travelers with tropical sprue, but therapy must be prolonged for 6 months or longer for residents of the tropics who have had long-term disease. Even with prolonged therapy, relapses have been seen in this population, although these may have been caused by reexposure to an infecting organism and represent recurrent rather than relapsing disease.[56] Reports have suggested that tropical sprue in the Caribbean is more amenable to therapy than sprue in India, but these studies are difficult to compare.[57] Poorly absorbed sulfa

drugs are an acceptable alternative to tetracycline in children or pregnant women.[58] A favorable symptomatic response to therapy with folate and antibiotics can provide additional evidence that tropical sprue was the cause of chronic diarrhea and malabsorption in a patient; however, even this is not specific because bacterial overgrowth in a blind loop syndrome would also be expected to respond. Lack of response to treatment should lead to additional diagnostic evaluation to include antibodies to gliadin or endomysium or small bowel biopsy.

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