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Tropical Sprue

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Abstract

Tropical Sprue has been a disease of decreasing significance over the past few decades. It's been postulated that easier access to antibiotics, improved sanitation and better hygiene practices around the globe may account for this apparent decline in frequency of cases seen today. Despite such speculation, it is unknown if the incidence of Tropical Sprue is truly declining, or if cases are simply being under-reported or perhaps even misdiagnosed. In reality, the current literature supports the theory that Tropical Sprue continues to be a significant cause of malabsorption in certain geographical areas of the world. This study aims to review the existing body of literature on Tropical Sprue and to provide a contemporary look into the disease and how it is managed today.

Keywords: Tropical Sprue (TS); Tropical malabsorption syndromes; Chronic diarrhea; Vitamin deficiency

Introduction

One of the more mysterious and still rather poorly understood diseases seen in the tropical regions of the world is Tropical Sprue (TS). TS is a clinical syndrome with an unknown etiology typically characterized by an acquired chronic diarrheal illness, small bowel mucosal abnormalities and malabsorption resulting in nutritional deficiencies and weight loss [1]. These are vague symptoms which can be produced by a large spectrum of diseases. Findings on endoscopy and histology can be non-specific which can make the diagnosis of TS challenging [2].

The first description of TS termed 'Idiopathic Malabsorption of the Tropics' was attributed to Dr. William Hillary who studied individuals with chronic diarrhea in Barbados in 1759 [3]. In his writings, he characterized the chronicity and relapsing nature of the disease as well as the findings of recurrent diarrhea, glossitis and wasting, all clinical features of TS. Whether the disease he was describing was truly TS has been disputed [4]. During the 20th Century, epidemic forms of TS have been documented in Burma, the Philippines, and in Bangladesh [5-7]. The disease was extensively studied throughout the 1960's and 1970's after an epidemic broke out in South India affecting as many as 100,000 people and killing approximately a third of those patients [8-10]. The research done during this period led to a better understanding of the disease, yet even today, many questions are still left unanswered.

With what little we know about TS, pinning down a specific definition has been difficult to do. Baker, in 1974, broadly defined TS as 'malabsorption of two or more substances in people in the tropics when other known cause have been excluded' [1,2]. More recently, Ghoshal, who has studied TS extensively over the past decade or so, has often quoted Klepstein's definition, which focused on very specific criteria. To meet these criteria, an individual must have: chronic small bowel diarrhea with malabsorption of two unrelated substances (ie. carbohydrates and fatty acids), abnormal small intestinal histology, exclusion of other known causes of malabsorption and persistent response to treatment [11,12]. Of importance with respect to the definition of TS is ensuring that the patient is symptomatic. Klepstein refined the definition to exclude asymptomatic, healthy individuals living in the tropics who demonstrate villous abnormalities [1]. Individuals with these characteristics are classified as having tropical enteropathy rather than TS. Those afflicted with tropical enteropathy demonstrate subclinical malabsorption but do not have diarrhea or show clinical evidence of malnutrition [13-16].

Epidemiology

TS is endemic in certain tropical regions of the world. Epidemic forms of TS are rarely seen today [16]. Seen primarily in adults, TS affects residents, expatriates and tourists of tropical regions classically including South East Asia, the Indian subcontinent, West Africa, Central America, South America, the Caribbean, and Puerto Rico [1,3,16,17]. TS is rarely seen in Eastern Africa, Jamaica, North America and Europe.

Over the years TS has been thought to be declining in incidence [16,18,19]. Some have speculated that this decline may be the result of increased accessability to antibiotics and better hygiene practices in these tropical areas. Bartholomew, in a review of TS in the Carribean, reported that over a period of 20 years the number of cases that had been documented in certain areas of the Carribean (namely Barbados, Puerto Rico and Cuba) were close to zero [19]. Beyond what has been shown in the Carribean, there is very little evidence to suggest that the overall incidence of TS is declining. Ghoshal, in a 2011 editorial, strongly opposed the theory that TS is on the decline [11]. The author cited under-reporting with a decline in the number of publications as the cause of this reported drop in incidence. Additionally, the actual number of cases of TS reported today may be underestimated. Post-infectious IBS (PI-IBS), a disease seen primarily in countries where TS is atypical (U.S, U.K., Korea and China), can present similarly to TS with chronic diarrhea, Small Intestinal Bowel Overgrowth (SIBO) and abnormal small intestinal permeability [20,21]. Most studies on post-infectious IBS have not excluded post infectious malabsorption syndrome, the epidemic form of TS. This observation suggests that it is probable that a proportion of those patients who participated in these studies may have had TS rather than PI-IBS.

More recently, studies in India have shown that TS is still a very

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problematic disease in that area of the world. In 2004 and again in 2012, a couple of studies sought to investigate the causes of malabsorption in Northern Indians [22]. Both found TS to be the number one cause of malabsorption in that particular geographical area. In another study from India in 2011, Dutta et al. [23] estimated the prevalence of TS to be as high as 29% in Southern Indians diagnosed with malabsorptive syndromes. TS led all other causes. Together, these studies suggest that TS is still the most common etiology of malabsorption seen in India.

Etiology

Though widely investigated, the exact causative agent of TS is still unknown. The current literature suggests that most are unsure if TS is its own distinct entity, a condition that simply results in SIBO or if it is somehow related to other disease states such as tropical enteropathy and post-infectious IBS [11,24]. Though there appears to be some overlap between these three entities given their clinical and histological similarities, there is no concrete evidence to suggest this is the case.

The most widely accepted theory today is that the syndrome appears to be due to a cascade of events, initiated through an enteric microbial infection [24]. The disease may start acutely or several months after an episode of gastrointestinal infection. This initial insult is thought to cause intestinal stasis leading to SIBO and enterocyte injury and dysfunction [25]. The term "post infective tropical malabsorption" has been coined to reflect this hypothesis that TS develops after an acute infectious diarrheal illness. Environmental factors, diet, and genetics have rarely been studied but may play a role in the acquisition of TS.

Pathophysiology

Slowing of small bowel transit time by a variety of mechanisms is thought to be a major contributor in the pathophysiology of this disease. The prolongation of orocecal transit time shown in patients with TS might be related to inhibition of proximal small bowel motility by malabsorbed fat passing through the distal small intestine [13,26,27]. The regulation of gastric and proximal small bowel (mostly jejunal) motility by fat in the distal small bowel is called "ileal brake", which is mediated by hormones such as peptide YY, enteroglucagon, neurotensin, and glucagon like peptide-1 (GLP-1). Patients with TS, who typically demonstrate an increase in unabsorbed fat in the intestinal lumen, have been postulated to have an exaggerated illeal brake from excessive release of the above mentioned mediators. The delay in orocecal transit time in these patients is thought to cause an increased exposure of the enterocyte to the bacteria in the tract resulting in enterocyte damage.

Some studies have suggested that part of the spectrum of disease seen in TS involves SIBO [26,27]. In bacterial overgrowth syndromes, enterocyte brush-border motility is altered [13]. Intestinal microbial overgrowth leads to increased plasma enteroglucagon and motilin which results in slowing of small intestinal transit, and may be responsible for enterocyte injury. It has been suggested that persistent infection may be responsible for the clinical syndrome associated with the disease. Contamination of the small bowel by aerobic enteric bacteria is seen with TS patients, but no specific causal agent has ever been found [13,16,26]. It has been proposed that after this enterocyte injury, there is a subsequent increase in luminal fatty acids, which causes release of enteral hormones like GLP2 to GLP-1 and GLP-2, among others. These mediators have been associated with the symptoms seen in TS because they are highly responsible for nutrient absorption by different mechanisms. GLP-2 is strongly related to gastric motility, gastric acid secretion and hexose transport that will ultimately increase the barrier function of the enteral epithelium. In contrast, GLP-1, as mentioned above, is one of the mediators for the ileal break mechanism.

Normal Small Intestinal Permeability (SIP) is necessary to maintain the physiological function of the small bowel whose primary role is to absorb nutrients. SIP is defective in several diseases with functional impairment of the small bowel such as Diarrhea-predominant irritable bowel syndrome (D-IBS), PI-IBS, Inflammatory bowel disease and Celiac disease [25]. These diseases, in addition to TS, can cause postdysenteric gut dysfunction that is thought to result from persistent low-grade inflammation in enteric submucosal and/or neuromuscular compartments. Theoretically, this inflammation can potentially lead to impaired enteric sensation and motility.

Clinical Manifestations

Villous damage and destruction results in demonstrable nutrient malabsorption. Like celiac disease, chronic profuse diarrhea, weight loss, steatorrhea, bloating, crampy abdominal pain, anorexia and weakness are typically seen in patients with TS [16,24]. Fever is atypical, having been seen more often in Indian populations than in Caribbean populations [7]. The diarrheal illness is generally mild but can sometimes be severe as well. The clinical course of TS is completely variable and can remit spontaneously or result in chronic malnutrition. It is important to note that malnutrition can occur without diarrhea [12]. The most common nutrient deficiencies are folate, vitamin B12, as well as lipid soluble vitamins (A, D, E, K). In India, folate deficiency is seen more than B12 deficiency, and in the Caribbean B12 deficiency tends to be the predominate deficiency [7]. Anemia, angular stomatitis, glossitis, dermatitis and osteopenia are some of the clinical manifestations associated with these nutritional deficiencies. Hypoproteinemia resulting in edema and electrolyte deficiencies including hypomagnesemia and hypophosphatemia have also been described in the literature. Although TS typically involves the entire small bowel, iron deficiency is rare in TS [16].

Diagnosis

TS is a diagnosis of exclusion. Though there are many causes of chronic diarrhea, TS should be considered higher on the differential with a history that includes chronic diarrhea with travel or previous residence in the endemic areas of the world. The hallmark finding of TS, malabsorption, can be diagnosed with a quantitative stool fat estimation and D-xylose testing [16]. In those who are asymptomatic with findings of mucosal abnormalities, tropical enteropathy should be strongly considered as a potential diagnosis. Tropical malabsorption alone has a large differential and includes celiac disease, lactase deficiency, inflammatory bowel disease, small intestinal bacterial overgrowth, tropical pancreatitis, intestinal scleroderma, amyloidosis, Immunoproliferative and Small-intestinal Disease (IPSID), and lymphoma [16,24]. HIV and other geographically relevant infectious etiologies should be ruled out. Mycobacterium tuberculosis, Strongyloides stercoralis, Giardia intestinalis, Entamoeba histolytica, Cryptosporidium parvum, Cyclospora cayetanesis, and Isosopora belli are some of the more commonly encountered pathogens that can result in chronic diarrhea and malabsorptive states in these particular areas of the world. If immunocompromised (ie. primary immunodeficiency vs. immunosuppressive therapy), opportunisitic infections must also be considered.

Endoscopically, the mucosa can be rather normal appearing or resemble celiac disease with scalloping of the duodenal folds [28,29]. On histology, villi tend to be partially blunted. Severe villous blunting,

a characteristic finding of celiac disease, is rarely seen with TS [30]. Other commonly observed findings include elongated crypts and inflammatory cells in the lamina propria [16,31]. Brown et al. in a recent study investigating the histological differences between TS and gluten sensitive enteropathies found that an eosinophilic-rich inflammatory infiltrate with intraepithelial lymphocytosis in the duodenal mucosa is suggestive of TS [32].

Once all other causes have been excluded, evidence of malabsorption of at least two different substances, in a symptomatic patient (i.e. chronic diarrhea, malnutrition) with villous abnormalities is highly suggestive of TS. Once a presumptive diagnosis is made, a response to treatment confirms the diagnosis of TS [24].

Treatment

In general, treatment consists of replacing electrolyte and vitamin deficiencies. Specifically, folate supplementation has been shown to be an effective treatment for TS. The typical regimen consists of 5-10mg/day of folic acid for 6 months, though longer duration of therapy may be necessary. Replacement with folic acid alone typically results in a fast recovery and can effectively reverse villous blunting [24,30]. If B12 deficient, supplementation is needed in addition to folic acid to completely reverse the macrocytic anemia that characteristically develops in these patients. Depending on the severity of the diarrhea, aggressive rehydration and electrolyte replacement are recommended. In those who do not respond to folic acid treatment alone, the addition of tetracycline (250 mg four times a day) or doxycycline (100 mg twice a day) for 3-6 months has shown to be beneficial as an adjunctive therapy [24]. Though for some unidentified reason(s), a proportion of those afflicted with TS living in southern India have been shown to be unresponsive to antibiotics [31]. Poorly absorbed sulfa drugs such as sulfaguanidine can be substituted in instances where tetracycline is contraindicated [32]. Probiotics have also been proposed as a potential therapy, however there are no current studies to back up these claims.

Response to treatment can take anywhere from weeks to months. Treatment success is variable and can be dependent upon a continued exposure or re-exposure to the endemic environment. For example, expatriates and those who have only visited endemic areas are more likely to experience complete resolution of their disease, usually with no recurrence. Alternatively, a proportion of permanent residents in Southeast Asia have demonstrated a poor response to conventional therapy, while those who reside in the Caribbean tend to respond to treatment initially but have a high rate of recurrence [24]. On occasion, TS has shown to be fatal if left untreated. In South India alone, mortality rates have been reported as high as 20% [24]. However, with the advent of newer antibiotics used for conditions like "traveler's diarrhea", mortality rates, though not extensively studied, are likely declining.

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