GASTROENTEROLOGY IN INDIA

Malabsorption Syndrome in India

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Introduction

Charaka, in or before the 6th century BC, may have provided the first recorded description of malabsorption syndrome when describing the disease called 'ghanati vyadhi'.1,2 The description runs as follows: The food instead of contributing to growth issues out of the body in a downward course. Whatever food a patient affected with 'ghanati vyadhi' takes is improperly digested. The person repeatedly evacuates stools that are sometimes watery, sometimes dry, sometimes consisting of undigested matter and frothy. While this description is consistent with any malabsorption syndrome, it is likely that it was in fact a description of primary malabsorption in the tropics or tropical sprue.

Tropical sprue is probably the most common malabsorption syndrome in India, and the history of research on malabsorption in our country is more or less synonymous with research on tropical sprue. In Western countries, the elucidation of physiology of intestinal absorption and the discovery of gluten hypersensitivity were factors that led to a significant amount of research on malabsorption. Research from India on malabsorption was slower to commence, concentrated predominantly on tropical sprue, and largely ignored the secondary causes of malabsorption.

The current review provides an overview of research from India on malabsorption syndromes till the present time. It is divided into four main sections, namely, establishment of norms for absorption studies in Indians, studies on tropical sprue, studies on other malabsorption syndromes, and malabsorption in children.

Absorption in normal Indian subjects

Absorption studies commonly include tests for absorption of fats, carbohydrates and vitamin B12. These have all been standardized for our population. Fecal fat excretion in Indians,3 the D-xylene urinary tests,4 vitamin B12 absorption,5 and the normal serum levels for iron, folate and vitamin B12 were all established.6 The 5 g dose of D-xylene has been advocated for use in our population because of problems with intolerance,6 but the 25 g dose has been used successfully by others.6 Serum D-xylene estimation has also been evaluated and standardized both in adults and children.6 Xylose absorption has been shown to be by passive transport rather than active transport, and is therefore a measure of surface area of the small bowel rather than epithelial cell damage, per se.5 Vitamin B12 absorption may be better estimated using a plasma sample for radioactivity in our population.4 This overcomes the problems with urinary collection in the Schilling test. Isotope breath tests for bacterial overgrowth have also been standardized in Indian subjects.10

Research on tropical sprue

Research on sprue in our country can be divided into two distinct phases. The first phase (essentially before 1970) saw clinical descriptions of the disease being published from various parts of India, while the second phase (generally 1965 and thereafter) was characterized by clinical research into the etiology and pathophysiology of sprue. Tropical sprue has been reviewed earlier in this Journal.11

Clinical and epidemiological descriptions

Although Charaka may have been the first to describe tropical sprue in Indians, in more modern times sprue was considered to be a disease of Europeans visiting India and the southeast Asian countries. The name 'Indische sprouw', given to this disease by the Dutch in the late 1700s, was Anglicized to tropical sprue by Manson.12 The disease was not uncommon among British soldiers in the Indian subcontinent during the Second World War.13 In the late 1950s, Baker described the syndrome in south India.14,15 The disease was subsequently reported from many other parts of the country in the 1960s.16,22 Tropical sprue, somewhat similar to that seen in India, had of course been simultaneously described from Puerto Rico, Haiti and Central America.

On epidemiological grounds, tropical sprue has been divided into three main categories:23

1. Sprue in expatriates from temperate climates
2. Endemic tropical sprue in indigenous populations
3. Epidemic tropical sprue in indigenous populations

Tropical sprue occurs sporadically in expatriates from temperate climates who have resided in the tropics for long periods of time. The onset of illness in these
individuals has usually been after a stay of one to two years in a tropical country. The clinical manifestations of sprue in these individuals are very similar to those of endemic sprue affecting the native population of tropical countries. More recently, tropical sprue in expatriates has been described in short-term overland travellers from Europe to the Indian subcontinent.

In the early part of this century, tropical sprue was thought to affect only visitors to the tropics. Subsequently, however, a sprue-like syndrome was described in Indians in Gujarat and Calcutta, and was named ‘parasprue’. Similar cases were recorded sporadically in Indian soldiers. In south India, tropical sprue affecting Indians was first recognized when investigation of patients with megaloblastic anaemia revealed that they all had malabsorption. Subsequently, endemic tropical sprue in Indians was described from all parts of India. Survey of an outpatient population in New Delhi revealed that the sprue syndrome was not uncommon, occurring in 0.2% of the population. Endemic sprue in Indians and sporadic sprue in Europeans have similar clinical manifestations, although it is possible that the etiology may be different.

Epidemics of tropical sprue were described in British troops and in Italian prisoners of war during the Second World War. Indian troops were also affected during these epidemics. In these subjects, malabsorption and its sequelae were present, but no etiological studies were carried out. Several large epidemics of sprue affecting villages in south India were described in the 1960s. In these epidemics, a high proportion of the population in affected villages were affected, the incidence being higher in adults than in children. The illness resolved in nearly a half of them within a month, while the others had illness of longer duration. Epidemic sprue differed from epidemic gastroenteritis in many respects.

Epidemic gastroenteritis affected children more often than adults, whereas children were relatively less often affected during epidemics of sprue. Epidemics of gastroenteritis tend to evolve and subside over a period of days to weeks whereas those of epidemic sprue developed over a one- to two-year period. Secondary and tertiary waves of sprue epidemics occurred in the originally affected villages after 5-10 years, sparing those who had been affected in the earlier wave. Malabsorption, which was persistent and encompassed more than one unrelated nutrient, was a common occurrence in epidemic sprue. On the other hand, persistent malabsorption especially of fat and vitamin B12 is uncommon in epidemic gastroenteritis. There were no clinical differences between epidemic and endemic sprue in southern Indians. A significant number of deaths were reported in early epidemics of tropical sprue in south Indian villages. These were apparently caused by fluid and electrolyte imbalance in the acute stage of the disease, when affected individuals failed to report for treatment. Detailed epidemiological studies revealed evidence of household and secondary transmission, suggesting that the disease was probably caused by an infective agent.

The years before 1970 were thus characterized by detailed clinical descriptions of the disease as it occurred in various parts of India.

The era of clinical research

Morphology and diagnosis

It was recognized early that subclinical malabsorption (or tropical enteropathy) was common among apparently healthy Indians. Tropical enteropathy did not usually involve malabsorption of more than one unrelated substance, was not progressive and was not clinically significant. In 1970, it was proposed that tropical sprue be defined as a syndrome characterized by jejunal morphologic abnormalities accompanied by malabsorption of two or more unrelated substances (in practice this meant fat, xylose, vitamin B12), in the absence of another cause for malabsorption. Since this definition mandated exclusion of other causes, it was not satisfactory.

The histology of small intestinal mucosa in patients with sprue has been described in detail in various studies. Three-dimensional reconstruction of the jejunal mucosa from a patient with sprue showed synchiae and bridge formation between villi, and it was suggested that the partial villous atrophy of sprue was due to fusion of villi. Ultrastructural studies of the small intestinal mucosa in sprue revealed a characteristic degeneration of the epithelial cells of the intestinal crypts. This ‘stem cell’ degeneration is seen in two other conditions — radiation enteropathy and graft-versus-host disease — but not in any other condition which has light microscopic appearances similar to tropical sprue. Therefore, detection of stem cell degeneration in the appropriate setting may be used to establish the diagnosis of tropical sprue.

Etiological studies

Despite much research, the etiology of sprue is still not clear. Epidemiological data from India suggest that tropical sprue is caused by an infective agent. However, to date, no single infective agent has been identified as the cause of sprue. Colonization of the small bowel by klebsiella or other coliform bacteria (Enterobacter cloacae, Escherichia coli) has been noted in some patients with tropical sprue in the Western hemisphere. These bacteria produce substances that cause fluid secretion when perfused through rat jejunal loops. These putative toxins were however not active in any of the conventional...
assays for enterotoxins, and have not been purified.46,47 There have been reports from parts of India that the small intestine of some patients with sprue is colonized by clostridia. Gorbich et al.48 detected clostridia in the small bowel of 3 of 6 patients with sprue in Calcutta. In south India, even apparently healthy subjects have bacterial contamination of the small bowel, and repeated studies have not demonstrated any significant excessive small bowel colonization by clostridia in patients with tropical sprue.49 Other studies, both from India and from other parts of the world, have failed to implicate clostridia colonization of the small bowel as the cause of sprue.50,51 This suggests that sprue in different parts of the world may have different causes.

Pleomorphic coronavirus-like particles have been observed in the feces of both healthy control subjects and some patients with sprue in southern India.52 In some patients with sprue, electron microscopy of jejunal mucosa revealed cytoplasmic inclusions suggestive of virus particles, possibly human enteric coronavirus.53 It is possible that this may represent one cause of sprue. However, attempts to purify these virus-like particles have met with no success.

Immunoglobulin concentrations in the intestinal mucosa and serum are unchanged in sprue.54,55 Assessment of immunological status in patients with sprue suggests that the enterocyte damage in sprue is not the result of a primary immunological process.55 Detailed morphometric studies revealed that intraepithelial lymphocytes were significantly increased in the crypts but not in the surface epithelium among patients with sprue. In epidemic cases, changes in lymphocyte behavior were detectable only after three weeks of illness, whereas mucosal lesions and malabsorption were already established during the first week.57 Although there is lymphocyte activation in sprue, this is probably secondary to enterocyte damage and an altered mucosal barrier.

Protein malnutrition (virtually no protein intake) induced intestinal mucosal atrophy which was reversible after reversal of protein malnutrition.58 In other studies in monkeys, protein restriction (5% compared to 18% intake in normal animals) induced 50% weight loss and hypoproteinemia after five months, which was associated with malabsorption of fat, xylose and vitamin B12.59 In these animals, intestinal histology was characterized by blunting of villi and elongation of some crypts, while other crypts remained normal. In addition, there was an inflammatory infiltrate in the lamina propria. It was suggested that malnutrition in association with unspecifed gastrointestinal infection may be responsible for the clinical syndrome of tropical sprue. On the other hand, the fact that protein deficiency is duration-related in sprue has been taken as indicative that it may be the result and not the cause of the disease.53

Pathophysiology of sprue
Alteration of organ function in sprue has been extensively investigated in India. Neurological and hormonal changes have been described in these patients.54-64 Changes in plasma lipids (decreased linoleic acid, raised monoenolic fatty acids, and the appearance of 5, 8, 11-eicosatetraenoic acid in the lecithin fraction), changes in albumin metabolism,56 excessive fecal loss of labelled bile acids,57 alterations in pancreatic exocrine function and altered disaccharidase activity58,70 have all been described. Abnormalities of gastric histology, secretory function, and of intrinsic factor production by the gastric mucosa have been described in sprue.71 Abnormal transport of nutrients by the small intestinal mucosa in sprue has been demonstrated by in vivo perfusion.72 Metabolic and transport activity of the intestinal epithelium is responsible for maintaining an acid microclimate at the mucosal surface which facilitates absorption of weak acids. In tropical sprue, studies have demonstrated an increase in the pH of mucosal surface of the jejunum, a factor that may contribute to altered intestinal function.73 Pecal bomb calorimetry is another technique that has been used to show that energy losses are increased in patients with sprue.74 In vitro incubation of small bowel mucosa with thymidine demonstrated increased crypt cell proliferation rates as well as increased loss of the label, suggesting that the cells were prematurely shed even in the crypt.75 Total intestinal transit time has been measured in sprue patients using radio-opaque markers,76 and found to be similar to that in healthy controls.

Several studies have attempted to identify the site and cause of excessive intestinal fluid losses in sprue. While fluid secretion into the jejunum was observed in patients with sprue in West Bengal,77 small bowel absorption of fluid in southern Indian patients with sprue was similar to that in healthy controls.78 In these subjects, absorbing water and electrolytes from the colon was defective.79 Subsequent studies showed that this defective absorption correlated with an excessive excretion of free unabsorbed fatty acids in the feces of these patients.80 Unabsorbed fatty acids are known to inhibit intestinal sodium-potassium-ATPase in vitro83 and alteration in large intestinal absorption was found to correlate with depresed sodium-potassium-ATPase activity in the colonic mucosa.82 Unabsorbed fatty acids inhibit colonic absorption when perfused in vivo in experimental animals, and this is associated with morphologic damage to the epithelium.83 Structural alterations have been noted in the rectal mucosa in tropical sprue,84,85 but it is not clear whether this is secondary to fatty acids and other toxic molecules, or is a primary manifestation of the disease.

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Reports of tetracycline therapy in sprue originated mainly from Puerto Rico and Haiti. Similar reports from India have been limited in number, sometimes without adequate controls. In the Indian studies, the response has been variable, with both poor and good responses being noted. In a small uncontrolled study, antibiotics with or without prednisolone resulted in clinical improvement, less obvious improvement in malabsorption, and little improvement in histology or biochemical markers of healthy enterocytes.

**Other malabsorption syndromes**

In contrast to tropical sprue, very little research has been done from India on other malabsorption syndromes. Celiac disease is well recognized in India Hypogammaglobulinemia with gastrointestinal presentation has been reported from India and is often associated with a malabsorption syndrome. Immunoproliferative small intestinal disease has been reported from India; this disease is not uncommon. Mediterranean patients who commonly have this disease are shown to have a characteristic rearrangement of the immunoglobulins genes in the lamina propria plasma cells implying a monoclonal proliferation of the cells. Preliminary studies on Indian subjects with immunoproliferative small intestinal disease have failed to demonstrate the presence of the gene rearrangement described above (unpublished observation). Studies are ongoing to determine whether there is a different alteration in these patients.

Intestinal parasites causing malabsorption include strongyloides, capillaria, the coecidian parasites and giardia. Giardiasis is common in India, but does not cause malabsorption in most infected subjects. In one study, treatment of children who were carriers of giardia did not result in any improvement in nutritional status. The role of parasites such as strongyloides, toxoplasma and cryptosporidia has not been systematically studied in India. Intestinal capillariosis, an infective cause of severe malabsorption previously unreported in India, has recently been described in an Indian who apparently acquired the infection by ingesting raw fish. Studies in patients with whipworm infection showed that they did not have any malabsorption.

Bacterial overgrowth syndromes have received passing attention. A study from New Delhi documented bile salt deconjugation in the small bowel of patients with intestinal tuberculosis and bacterial overgrowth. While this provides additional explanation for malabsorption in this situation, no attempt was made to isolate the anaerobes that might be responsible.

Small bowel absorption may be secondarily affected in systemic disease. In pellagra, defective absorption of more than one unrelated substance was noted in nearly 60% of patients studied. On the other hand, patients with leprosy, both lepromatous and tuberculoid, did not have a higher incidence of absorption defects than the normal Indian population. Malabsorption syndromes that have not received serious attention in India include the malabsorption of chronic pancreatitis and that following gastric surgery.

**Malabsorption in children**

Malabsorption in children deserves special attention because of the different spectrum of diseases causing malabsorption in this age group. D-xylose absorption has been evaluated in children and tolerance testing confirmed that the peak blood value in normal children was reached 60 min after ingestion of the xylose dose. Tropical sprue was originally thought to be very rare in children. However, sprue is now well recognized to occur in children in India. The disease in children occurs in both epidemic and endemic forms, although the latter often spares children. The clinical and laboratory manifestations are very similar to those in adults and treatment is also similar. Celiac disease is now known to be a common cause of malabsorption in children, particularly in northern India. In one study, of 62 children with chronic diarrhea, 21% had celiac disease, 10% had cystic fibrosis and 5% had endemic tropical sprue. A recent survey from the same center studied children with diarrhea of more than three weeks and one or more abnormal absorption study. Using these criteria, the most common identified cause was protracted diarrhea (33%), followed by celiac disease (27%), parasitic infestations (9%), milk protein intolerance (6%) and tuberculosis (5%). A series of patients with cystic fibrosis has been described and the clinical features are similar to the disease in Western children. Subclinical malabsorption has also been reported in some children with mild to moderate (grade 1-2) protein-energy malnutrition. A 12-year-old child with hypogammaglobulinemia with malabsorption has also been reported.

In conclusion, this review gives an overview of research on malabsorption syndromes in India. This research peaked in the late 1970s and early 1980s and is now declining, but may well be resurrected if HIV infection increases to epidemic proportions in India.

**References**


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