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ORIGINAL ARTICLE

Current spectrum of malabsorption syndrome in adults in India

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Abstract
Aim Tropical sprue was considered to be the most important cause of malabsorption in adults in India. However, several reports indicate that celiac disease is now recognized more frequently.
Methods We analyzed the clinical presentation, endoscopic and histological features of 94 consecutive patients (age >12 years) with chronic diarrhea and malabsorption syndrome. The spectrum of disease in these patients and features differentiating celiac disease and tropical sprue are reported here.
Results Celiac disease (n=61, 65%) was the most common cause of malabsorption followed by tropical sprue (21, 22%). Other conditions including cyclosporiasis (3), Crohn's disease (2), common variable immunodeficiency (2), lymphangiectasia (1), William's syndrome (1), and idiopathic malabsorption (3) accounted for the remainder. A greater number (21, 34%) of patients with celiac disease than those with tropical sprue (4, 19%) presented with atypical manifestations. Patients with celiac disease were younger (p=0.001), more often had anemia, (p=0.001), scalloping of folds (p=0.001), moderate (p=0.02) or severe (p=0.001) villous atrophy, higher grade of intraepithelial lymphocytic infiltration (p=0.001), crypt hyperplasia (p=0.001), cuboidal (p=0.001) and pseudostratified (p=0.009) surface epithelial cells, and diffuse (p=0.001) epithelial damage. In comparison, patients with tropical sprue were older and more often had normal duodenal folds, normal villi, tall columnar epithelial cells and focal epithelial damage.
Conclusions Celiac disease was the most frequent cause of malabsorption syndrome in this series of patients. There are significant clinical and histological differences between celiac disease and tropical sprue.

Keywords Celiac disease · Chronic diarrhea · Tropical sprue · Villous atrophy

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Introduction

The etiology of malabsorption syndrome varies according to the geographical location and age of the patients [1, 2]. While celiac disease, Crohn's disease, cystic fibrosis, and intestinal lymphangiectasia are the frequent causes of malabsorption syndrome in the West, tropical sprue, parasitic infections, intestinal tuberculosis, and primary immunodeficiency syndromes have been reported to be the commonest causes of malabsorption syndrome in the

developing countries, like India [3–5]. With improvement in socioeconomic status, sanitary conditions and increasing use of antibiotics in recent years, the incidence of tropical sprue has declined. On the other hand, celiac disease is increasingly recognized as an important cause of malabsorption both in children [6–8] and adults [9–11]. Only half of adult patients with celiac disease present to a physician with typical clinical manifestations; the rest present with atypical manifestations, such as short stature, refractory anemia, or metabolic bone disease [12, 13].

Clinical features and histological features are similar in patients with celiac disease and tropical sprue. With emergence of celiac disease in developing countries, it is important to know the differentiating features between celiac disease and tropical sprue. The aim of this study was to present the current spectrum of patients with malabsorption at a tertiary care center. We also report the differences in the clinical, endoscopic, and histological features between patients with celiac disease and tropical sprue.

Methods

Patients

One hundred and twenty-seven patients (age >12 years) with chronic diarrhea (diarrhea lasting for more than 4 weeks) and malabsorption syndrome attending the Gastroenterology OPD between May 2006 and March 2009 were enrolled. These included patients referred from Hematology, Endocrinology, and Gynecology departments. The diagnosis of malabsorption was made when any two of the following features were present: (1) abnormal D-xylose test, (2) presence of anemia and/or hypoalbuminemia, and/or (3) clinical features suggestive of nutritional deficiencies (iron, folate, vitamin D). Patients with lactose intolerance (based on clinical suspicion and a positive lactose hydrogen breath test) and irritable bowel syndrome (based on Rome II criteria) were excluded from this study. Patients who received anti-parasitic drugs during the past 2 weeks and those showing non-compliance to follow up were also excluded. Of the total patients, five patients had primary lactose intolerance and were excluded. Four patients (2 each with celiac disease and tropical sprue) had secondary lactose intolerance and were included. Thus, 94 patients (59 men), in whom all relevant investigations were available, were included in the final analysis. Of these 94 patients, 28 were between 12 and 18 years of age.

Demographic and clinical features including age, gender, duration of the disease, frequency of stools/day, consistency of stools, presence/absence of blood and mucus, abdominal pain, vomiting, and fever were recorded. Hematological and biochemical investigations including liver function, renal function, fasting blood sugar, serum calcium, and phosphorus levels were performed for all patients.

Tests for absorptive functions

Urinary excretion of D-xylose was measured after an oral dose of 5 g of D-xylose and excretion below 1 g/5 g/5 h was considered abnormal [14]. Fecal fat was estimated by Van de Kamer quantitative method and fecal fat content >7 g/day in adults was taken as abnormal [15].

Stool examination

Three consecutive stool samples from the patients were obtained and examined for non-pathogenic and pathogenic parasites including coccidia. The stool samples were concentrated by formol-ether concentration technique, according to standard methods [16]. Direct microscopic examination of fecal specimens was performed in fresh physiologic saline and Lugol's iodine. Stool samples were also stained by modified Kinyoun's acid-fast (MAF) staining for coccidian oocysts using the standard protocol [17]. Micrometry was done in case of any ambiguity in confirming the size of coccidian oocysts.

Serological tests

All patients underwent either anti-tissue transglutaminase antibody (anti-tTG Ab; ELISA kit from Binding Site Limited, Birmingham, UK) or anti-endomysial antibody (EMA) by indirect immunofluorescence test using monkey esophagus as substrate and rabbit antihuman IgA isotype as conjugate antibody (DAKO PO204, Carpinteria, CA), tests for celiac disease [18]. Serum immunoglobulin level (IgA, IgG, and IgM) estimation (using ELISA) was performed for patients who were suspected to have celiac disease, but had a negative serological test. Wherever clinically indicated, patients underwent screening for antibodies to HIV-1 and HIV-2 and thyroid function tests.

Glucose hydrogen breath test

Glucose hydrogen breath test (GHBT) was done using Quintron Microlyzer, Milwaukee, USA. An increase of 12 ppm in the breath hydrogen excretion at 2 h above baseline was considered positive test for bacterial overgrowth. GHBT was done in 4 patients only where there was a clinical suspicion of bacterial overgrowth.

Endoscopy and mucosal histology

Upper gastrointestinal endoscopy was done for all the patients, and the status of the duodenal folds was recorded

(normal, attenuation, and scalloping of mucosal folds). Biopsies were analyzed for mucosal changes by two pathologists (SDG, PD) with special interest in gastrointestinal pathology. The modified Marsh grading system was used for grading mucosal changes: Grade 0, normal histology; Grade 1, increase of intraepithelial lymphocytes (IEL) [lymphocytes >40/100 enterocytes]; Grade 2, increased IELs along with crypt hypertrophy or a Crypt (C): villous (V) ratio of >1; and Grade 3, increased IELs along with crypt hypertrophy and variable degree of villous atrophy [19]. A further semi-quantitative classification was performed as follows: grade 3a, C: V ratio of 1:3 or 1:2; grade 3b, C: V ratio of 1:1; and grade 3c, C: V ratio of >1 (normal C: V ratio was taken as 1:4) [19]. The nature of the mucosal epithelial cells, that is, tall columnar, short columnar, cuboidal, or atrophic was recorded. The villous tip predominant pattern of IELs was described as 'crescendo' and the crypt predominant IELs pattern was described as 'decrescendo'. IELs were further sub-classified as follows: 1+, IELs >40 but ≤60/100 enterocytes; 2+, IELs ≥60 but ≤80/100 enterocytes; 3+, IELs ≥80/100 enterocytes. The type and density of inflammatory infiltrate in lamina propria was recorded [20]. Associated thickening of basement membrane of the mucosal epithelium and morphological evidence of megaloblastosis (significant nucleomegaly and opened up chromatin in the epithelial cell nuclei) were carefully looked for.

Diagnostic criteria for causes of malabsorption

The diagnosis of celiac disease was made on the basis of a modified European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criterion [21], that is, suggestive clinical manifestations, suggestive histology, and unequivocal response to gluten free diet. In addition, a positive serological test (tissue transglutaminase antibody and/or anti-endomysial antibody) was also considered in this subset. The diagnosis of inflammatory bowel disease (IBD) was based on European Crohn's and Colitis Organization (ECCO) criteria [22]. The diagnosis of Crohn's disease was made on the basis of a combination of clinical, endoscopic, and histological features and the extent of the disease was evaluated by colonoscopy, small intestinal imaging (BMFT, small bowel enteroclysis or CT enteroclysis). Duodenal biopsies were done whenever there was a clinical suggestion of malabsorption. Common variable immunodeficiency was diagnosed by the presence of low serum globulins and immunoglobulins (IgG, IgA, and IgM) levels. Intestinal lymphangiectasia and hypothyroidism were diagnosed based on the presence of dilation of lacteals in the lamina propria and abnormal serum thyroid stimulating hormone TSH levels, respectively. Coccidiosis or giardiasis was diagnosed on the basis of light microscopy, presence of parasite in the stool and response to treatment. Histological evidence of clusters of protozoa in proximity to mucosal epithelial surface, or identification of coccidia either in the surface of epithelium or internalized in the cell cytoplasm was taken into account. The diagnosis of tropical sprue was made on the basis of the presence of chronic diarrhea, malabsorption, exclusion of other causes, and a persistent response to antibiotics [2]. When no other cause was found, it was labeled as idiopathic malabsorption.

Management

Patients with celiac disease were put on a gluten free diet and nutritional supplements under the guidance of a nutritionist. Patients with tropical sprue were treated with doxycycline for 6 months along with folic acid [23, 24]. Patients with Crohn's disease were treated with mesalamine and immunosuppressive drugs. Patients with common variable immunodeficiency were treated with episodic infusion of immunoglobulins. Patients with intestinal lymphangiectasia and zinc deficiency were treated with medium chain triglycerides and zinc supplementation, respectively. Patients were followed up at the interval of 1–3 months.

Results

The demographic, clinical, biochemical, endoscopic, and histological characteristics of patients included in this study are shown in Table 1. The mean duration of diarrhea was 88.5 (85.7) (Range: 1.5, 360) months.

Etiology of malabsorption syndrome

The most common cause of malabsorption was celiac disease (n=61, 64.9%) followed by tropical sprue (21, 22.3%). Of the 61 patients with celiac disease, 22 were between the age of 12 and 18 years. Other causes of malabsorption syndrome in this study were cyclosporiasis (3), common variable immunodeficiency (2), Crohn's disease (2) intestinal lymphangiectasia (1), William's syndrome (1) and idiopathic malabsorption (3).

Differentiation between celiac disease and tropical sprue

Clinical features and serology

Patients with celiac disease were younger than those with tropical sprue (mean [SD] age at presentation 21.8 [8.4] years vs. 34.3 [13.8] years; p=0.001). A significantly higher number of patients with celiac disease had anemia

Table 1 Demographic, clinical and biochemical features of patients with celiac disease and tropical sprue

Parameters		Celiac disease (n=61)	Tropical sprue (n=21)	p-value
Age (years)		21.8 (8.4)	34.3 (13.8)	0.001
Male: Female ratio		37:24	13:8	1:00
Duration of diarrhea (mo) (median [range])		60 (3–300)	21 (2–360)	0.09
Clinical features	Abdominal distension	22 (36.1)	5 (23.8)	0.45
	Vomiting	12 (19.7)	2 (9.5)	0.50
	Weight loss/failure to gain weight	36 (59.0)	14 (66.7)	0.72
	Anemia (hemoglobin <12.0)	54 (88.5)	11 (52.4)	0.001
	Short stature	13 (21.3)	1 (4.8)	
	Type I diabetes mellitus	2 (3.3)	1 (4.8)	
	Secondary infertility/delayed menarchy	3 (4.9)	2 (9.5)	
	Hypothyroidism	4 (6.6)	0 (0)	
	Chronic liver disease	1 (1.6)	0 (0)	
	Dermatitis herpetiformis	1 (1.6)	0 (0)	
Investigations	Hemoglobin (gm/dL)	8.8 (2.8)	10.9 (2.9)	0.004
	Total protein (g/dL)	7.6 (0.9)	7.9 (0.8)	0.09
	Serum albumin (g/dL)	4.3 (0.6)	4.4 (0.7)	0.82

Data are as number (%) or as mean (SD)

compared to those with tropical sprue (88.5% vs. 52.4%) (p=0.001). Extra-intestinal manifestations, such as short stature, delayed menarche, and secondary infertility and associated diseases, such as hypothyroidism, diabetes mellitus, and chronic liver disease were higher in patients with celiac disease than in those with tropical sprue, though this was not significant (Table 1).

Celiac serology test was performed in all patients except those with Crohn's disease. Of 61 patients with celiac disease, anti-tTG Ab was positive in 59. The two with negative anti-tTG Ab, however, had positive EMA Ab.

Endoscopy and histology

Most patients with tropical sprue had normal duodenal folds (85.7%) while, the appearance of duodenal folds was abnormal in 82% patients with celiac disease. Scalloping of folds and both scalloping and attenuation of duodenal folds were more frequently present in patients with celiac disease (Table 2).

On histological examination, while none of the patients with celiac disease in this study had Marsh grade 0 and 1 villous atrophy; 1 (4.8%) and 9 (42.8%, p=0.001) patients with tropical sprue either had grade 0 and grade 1 mucosal changes, respectively. All patients with celiac disease had Marsh grade 3 villous atrophy whereas 11 patients with tropical sprue had Marsh grade 3 atrophy. Crypt hyperplasia was higher in celiac disease than in tropical sprue (p=0.001).

While increase in IELs were noted in all the biopsies; grade 3 IEL infiltrates was seen only in celiac disease. The crescendo and decrescendo patterns of IEL infiltrates were identified in both the diseases. The extent of epithelial cell damage in the biopsies was focal in most (85.7%) patients with tropical sprue, the extent of epithelial damage was mostly diffuse in those with celiac disease. The normal tall columnar shape was maintained in most patients with tropical sprue, and changed from normal tall columnar epithelium to cuboidal cells in 40.9% of patients with celiac disease (Figs. 1 and 2).

The density of lamina propria inflammation and type of inflammatory cell infiltrate were similar in tropical and celiac sprue (Table 2).

Parasites

Pathogenic or non-pathogenic parasites were detected on stool examination in 34 (36.2%) patients with chronic diarrhea and malabsorption. Parasitic infestations were found in 17 (28%) and 5 (24%) patients with celiac disease and tropical sprue, respectively. The parasites detected in celiac disease were *Giardia lamblia* (n=12), *Entamoeba histolytica* (3), *Cyclospora cayetanensis* (1), helminthes (1); those detected in tropical sprue were *G. lamblia* (1), *E. histolytica* (1), helminths (3). Two patients with tropical sprue infected with *G. lamblia* and *T. trichura* were treated; however, there was no response to anti-parasitic drugs. These patients were then treated with antibiotics and in view of the response to treatment were diagnosed as tropical sprue [25].

Discussion

In the present study, celiac disease was the most common cause of malabsorption syndrome, followed by tropical sprue.

Table 2 Endoscopic and histological features of patients with celiac disease and tropical sprue

Parameters		Celiac disease (n=61)	Tropical sprue (n=21)	p-value
Endoscopic features: Pattern of duodenal mucosa	Normal folds	11 (18.0)	18 (85.7)	0.001
	Attenuated folds	16 (26.2)	3 (14.3)	0.37
	Scalloped folds	30 (49.2)	0 (0)	0.001
	Attenuated and scalloped	4 (6.6)	0 (0)	0.57
Histologic features				
Villous atrophy (Marsh's criteria)	Grade 0	0 (0)	1 (4.8)	0.26
	Grade 1	0 (0)	9 (42.8)	0.001
	Grade 2	0	0	–
	Grade 3a	11 (18.0)	8 (38.1)	0.06
	Grade 3b	27 (44.3)	3 (14.3)	0.02
	Grade 3c	23 (37.7)	0 (0)	0.001
Lamina propria inflammation	Normal	0 (0)	0 (0)	–
	1+	6 (9.8)	2 (9.5)	0.99
	2+	44 (72.1)	18 (85.7)	0.25
	3+	11 (18.0)	1 (4.8)	0.17
Epithelial cell apparatus	Tall columnar	15 (24.6)	17 (80.9)	0.001
	Low columnar	21 (34.4)	4 (19.0)	0.27
	Cuboidal	25 (40.9)	0 (0)	0.001
	Pseudostratified	15 (24.6)	0 (0)	0.009
	Loss of goblet cells	60 (98.4)	19 (90.5)	0.16
Extent of epithelial damage	Focal	11 (18.0)	18 (85.7)	0.001
	Diffuse	50 (81.9)	3 (14.3)	
Predominant localization of IEL	Crescendo	56 (91.8)	18 (85.7)	1.00
	Decrescendo	5 (8.2)	3 (14.3)	
Types of inflammatory cells				
Polymorphonuclear				
	Grade I	17 (27.9)	4 (19.0)	0.57
	Grade II	11 (18.0)	2 (9.5)	0.49
	Grade III	1 (1.6)	0 (0)	0.99
Lymphocytes				
	Grade I	57 (93.4)	21 (100)	0.57
	Grade II	2 (3.3)	0 (0)	0.99
	Grade III	1 (1.6)	0 (0)	0.99
Plasma cells				
	Grade I	48 (78.7)	19 (90.5)	0.33
	Grade II	6 (9.8)	0 (0)	0.33
	Grade III	7 (11.5)	2 (9.5)	0.99
Eosinophils		27 (44.3)	15 (71.4)	1.00
Presence of mucosal edema		23 (37.7)	12 (57.1)	0.19
Megaloblastic changes	Present	8 (13.1)	2 (9.5)	1.00
	Absent	53 (86.9)	19 (90.5)	
Thickened basement membrane		7 (11.5)	0 (0)	0.18

Data are as number (%) or as mean (SD)

The study is consistent with our earlier report [25]. Celiac disease is not a rare entity in India. Also, the perception that tropical sprue is becoming extinct in India is also not true. In a study from Lucknow, tropical sprue accounted for 39.3% of patients with malabsorption syndrome [3].

A low index of suspicion and reliance on classic symptoms may have resulted in under-diagnosis of celiac disease in India until now. Sood et al. [26] reported a rising incidence of celiac disease in their hospitalized patients with celiac disease over the last 10 years. In recent years,

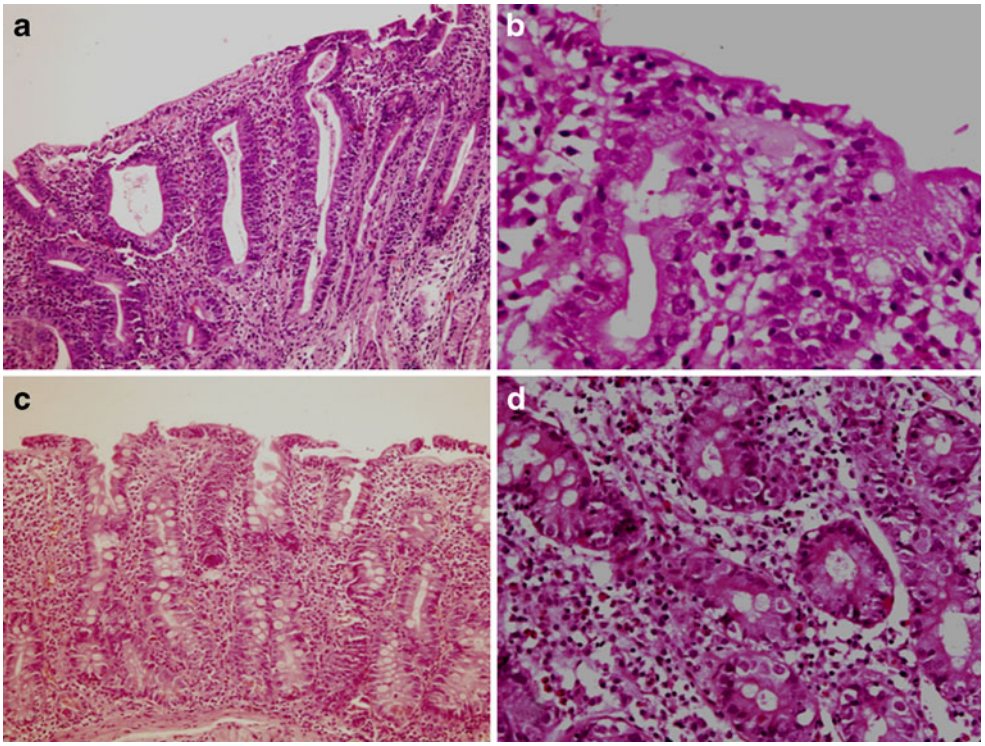

Fig. 1 Photomicrographs from a duodenal biopsy with celiac disease show markedly increased IELs, with flattening of villi and crypt hyperplasia (Fig. 1a, H, and E x 40). The mucosal surface epithelium shows IELs and low cuboidal cells (Fig. 1b, H, and E x 200). Mucosal biopsy shows "crescendo" pattern of IEL infiltration, that is, the intra-epithelial lymphocytes is predominantly seen towards the tip of the villi (Fig. 1c, H, and E x 40). There is a mixed inflammatory cell infiltrate in lamina propria along with edema (Fig. 1d, H, and E x 200)

celiac disease is being reported more frequently in India not only in children but also in adults [6, 7, 9–11]. There are many misconceptions which may contribute to under diagnosis of celiac disease in India including the belief that it is a disease of children. It is not recognized that children, in whom diagnosis was missed or undiagnosed, will present in adulthood with either typical or atypical manifestations [12, 13, 27]. Further, it was believed that celiac disease is a disease of the European nations and was uncommon in our part of the world [28].

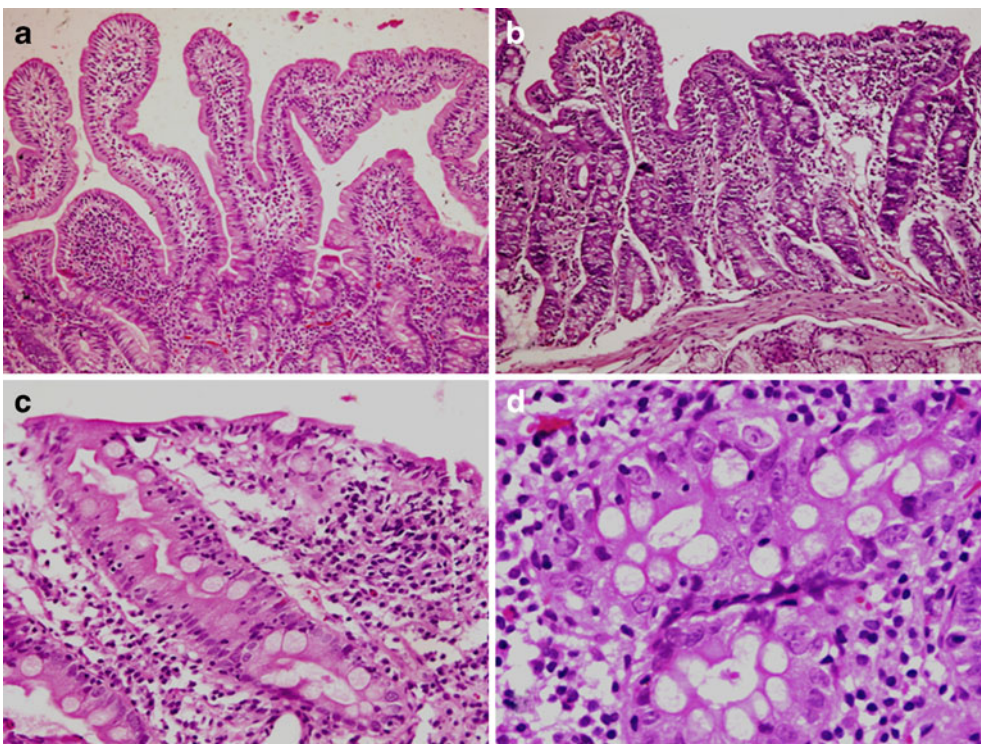

Fig. 2 Photomicrographs from duodenal biopsies with tropical sprue show normal (Fig. 2a, H, and E x 40) to mild villous atrophy (Fig. 2b, H, and E x 40). The IELs are predominantly crypt centric (Fig. 2c, H, and E x 100). Occasionally, the epithelial cell nuclei show megaloblastic changes (Fig. 2d, H, and E x 400)

Moderate-to-severe villous abnormalities are not required for diagnosis of celiac disease, as shown by the varying states of evolution from Marsh 1 to Marsh 3 grades with mild, moderate, or severe villous abnormalities [29]. Bhatnagar et al. have shown that 25% of children with chronic diarrhea and with mild villous abnormality have celiac disease [7]. Although there is an overlap of histological features between the two diseases, severe IEL infiltration, severe villous atrophy, and significant crypt hyperplasia are seen more commonly in celiac disease. Crypt-centric IELs have been described as one of the diagnostic parameter in favor of tropical sprue; in our study the crescendo and decrescendo patterns occurred equally in both the diseases [30]. A combination of clinical, serological, and histological features can differentiate celiac disease from tropical sprue.

There are many possible reasons for a decrease in the prevalence of tropical sprue which includes better sanitation, better hygiene, a decrease in water borne diseases, and early diagnosis of bacterial or infective illnesses [24]. As tropical sprue was previously a diagnosis of exclusion, many patients with other etiologies of malabsorption syndrome could have been misdiagnosed as tropical sprue. With better diagnosis and awareness, the apparent prevalence of celiac disease may have increased thereby shrinking the basket of tropical sprue. Although there is a lack of epidemiological evidence, the hygiene hypothesis may explain a decline in tropical sprue [31].

In conclusion, celiac disease was the commonest cause of malabsorption syndrome in this series from India. There were significant clinical and histological differences between celiac disease and tropical sprue.

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