Original Article

Evaluation of Small Intestinal Biopsies in Malabsorption Syndromes

Ashmeet Kaur[1]*, Poojaba Jadeja[2], Neha Garg[2], SML Rai[2] and N. Mogra[2]

[1]Department Of Pathology, Santokba Durlabhji Memorial Hospital, India
[2]Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, India

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ABSTRACT

Backgound: The gold standard test for evaluation of intestinal malabsorption is biopsy. The varied yet similar, abnormal mucosal architecture patterns in intestinal malabsorption makes it difficult for the pathologist to report its etiological cause

Methods: We analyzed the clinical presentation, endoscopic and histological features of 328 consecutive patients with complaints suggestive of malabsorption syndrome. The spectrum of disease in these patients were studied and divided into four groups on the basis of histologic features and correlated with clinical/endoscopic findings

Results: Group1 were entities usually associated with a diffuse severe villous abnormality and crypt hyperplasia ,all 57 cases were of celiac disease (17.3%), Group 2 were entities usually associated with a variable villous abnormality and crypt hypoplasia, included 7 cases-malnourished 5(1.5%) and post chemotherapy 2(0.6%), Group 3 were entities usually associated with a nonspecific variable villous abnormality, usually not flat included 252 biopsies- Tropical sprue 16(4.8%), nonspecific duodenitis/jejunitis/ileitis 212 (64.6%), peptic duodenitis 16(4.8%), intestinal tuberculosis 8 (2.43%), and in Group 4 were entities associated with variable villous abnormalities illustrating specific diagnostic changes included 12 cases-giardiasis 2 (0.6%), Crohn's disease 8 (2.4%), intestinal lymphangiectasia 1 (0.3%), lymphoma 1(0.34%).

***Corresponding author:**
Dr Ashmeet Kaur, Department Of Pathology, Santokba Durlabhji Memorial Hospital, India
Phone: +91 9680027604
Email: ashmeetkochar@gmail.com

Introduction

The etiology of malabsorption syndrome varies according to the geographical location, age and vary over time .[1,2,3] 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.[3] In the past, tropical malabsorption, popularly known as tropical sprue, was a common cause of epidemics in southern Indian villages.[3]

Histologically, varied spectrum of morphology is observed. Gastrointestinal tract infections are extremely common in a developing country like India because of poor hygienic conditions but it is also noticed that specific infections such as giardiasis or tuberculosis are not more frequent. Pathologists often report nonspecific inflammation may be due to chronic gastric mucosal irritation (with drugs),or gastrointestinal tract infections, we tend to give a diagnosis of mild nonspecific duodenitis if we see even few lymphocytes or plasma cells in the lamina propria . Quite often we miss important diagnosis like celiac disease presuming its low prevalence in adults and in a developing country like India.

The aim of this study was to evaluate the histological features 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 other causes of malabsorption.

Material and Methods

Overall 328 patients of malabsorption were enrolled in study during Jan 2012-Aug 2015 and were evaluated to ascertain the etiology of disease process and managed as per need. These included all patients consecutively attending Gastroenterology Clinics, referred from medicine & pediatrics-indoors & outdoors after basic workup. The diagnosis of malabsorption was made on the basis of the following features: (1) Diarrhea, vomiting/abdominal pain or clinical features suggestive of nutritional deficiencies (iron, folate, vitamin D), and/or (2) presence of anemia and/or hypoalbuminemia and/or (3) Abnormal endoscopic finding. Patients with lactose intolerance and irritable bowel syndrome and those showing non-compliance to follow up were excluded from this study. Thus, 328 subjects (195 men), in whom all relevant investigations were available, were included in the final analysis.

Demographic and clinical features including age, gender, duration of the disease, frequency of stools/day, consistency of stools, abdominal pain, and vomiting were recorded. Hematological and biochemical investigations including hemoglobin, total protein , liver function test and thyroid function test (if required).Upper gastrointestinal endoscopy was done for all the patients, and the status of the duodenal folds was recorded (normal, attenuation, scalloping of mucosal folds, erythema/ulcers and thickened).

Biopsies were analyzed for mucosal changes by two pathologists and were divided into four groups on the basis of histologic features. Group 1- diffuse severe villous abnormality and crypt hyperplasia **,** Group 2- variable villous abnormality and crypt hypoplasia Group 3- nonspecific variable villous atrophy , usually not flat and Group 4 **-**variable villous abnormalities illustrating specific diagnostic changes.[4]

Data thus collected were entered in excel sheet and were subjected for statistical analysis. Continuous variables were summarized as mean and standard deviation, while categorical and nominal variables were summarized as percentages. Unpaired t test and ANOVA test with Post Hoc Tukey HSD test were used for comparing continuous variable while nominal and categorical variable were compared by chi-square test. Agreement between grades were measured and analysed by using kappa statistics.

Diagnostic Criteria for Causes of Malabsorption: The diagnosis of celiac disease was made on the basis of clinical manifestations, biochemical (ttG), endoscopic finding ,specific histologic changes and response to gluten free diet. The diagnosis of celiac disease was graded by Ensari criteria which require presence of duodenal mucosal biopsy changes. Patients with diarrhea, malabsorption of two or more substances, after exclusion of other causes, and a persistent response to antibiotics, were diagnosed to have tropical sprue. Intestinal tuberculosis was diagnosed in presence of acid fast bacilli on mucosal biopsy or presence of caseating granuloma on biopsy specimen. Crohn's disease was diagnosed using a combination of histology, endoscopic, radiological, histological features and response to treatment. On all the biopsies in this group, stool examination was carried out and parasitosis was detected by microscopic examination of stained stool smears. Specific abnormality like intestinal lymphangiectasia was detected on the basis of clinical history, biochemical parameters and histology. When no other cause was found but lamina showed inflammation, it was labeled as non specific inflammation.

Results

Out of the total 328 biopsies, 238 were from duodenum, 74 were from jejunum and 13 were from ileum and 3 resected specimens. The mean duration of diarrhea was 136.48 days (range 10days-720days)

Etiology of Malabsorption Syndrome: Subjects included in group1 were 57, in group 2 were 7, in group 3 were 252 and in group 4 were 12.The most common cause of malabsorption was nonspecific duodenitis/ jejunitis/ ileitis (n=212,64.6%), followed by celiac disease (n=57,17.3%). Other causes of malabsorption in this study are illustrated in figure 1.

From table **2**, we concluded that patients with celiac disease were younger than those suffering from any other cause of malabsorption(32.58, p=0.005). Although patients suffering from Tropical sprue, Intestinal tuberculosis and nonspecific inflammation (40.60) presented with almost similar age as those with crohns, lymphoma or lymphangiectasia (38.7), it was not a significant finding.

Majority of the subjects presented with diarrhea (52.3%) and the mean duration of diarrhea was 136.48 days(range=10-720 days).Other minor complaints of presentation were abdominal pain, vomiting, weight loss and dyspepsia. Duration of diarrhea was maximum in subjects of celiac disease, though not significant. Hemoglobin, platelet count and total protein were lowest in malnourished and post therapy patients, although not significant

Demographic,Clinical and Laboratory data comparison: Patients with celiac disease were younger than those with nonspecific duodenitis (mean age at presentation 32.58 years vs 40.02 years), though statistically not significant. More number of patients with celiac disease had anemia compared to those with nonspecific duodenitis (42.10% vs 39.6%) (p< 0.001) as in table 3. Total protein although relatively low in celiac disease patients compared to non specific inflammation , statistically insignificant.

Associated diseases like hypothyroidism were higher in patients with celiac disease than in those with nonspecific (10.52% vs 7.1%), though not significant.

Duration of diarrhea was observed to be more in patients with celiac disease(219.01 days vs 108.64 days) (p=0.005)

Endoscopy and Histology: Most patients with nonspecific duodenitis had erythematous duodenal folds with/without ulcers (38.6%) while, the appearance of duodenal folds was scalloped in 54% of patients with celiac disease as seen in table 4 .

Scalloping of folds (54.3%) and both scalloping and attenuation (21%) of duodenal folds were more frequently present in patients with celiac disease.

On histological examination, while 17 (29.8%)patients with celiac disease in this study had normal/ mild villous atrophy, 55 (25.94%,p) patients with nonspecific duodenitis had normal/mild villous atrophy. 19(33.34%) and 22 (38.54%) patients with celiac disease had moderate and severe villous atrophy, 29 (13.67%) & 7(3.3%) patients with nonspecific duodenitis had moderate and severe villous atrophy, respectively. Crypt hyperplasia was higher in celiac disease than in non specific duodenitis. (p<0.001). Histologically, IELs were highest in subjects of celiac disease among all groups (32.8,p<0.01)

Table 1: Abnormal mucosal architecture in different diseases causing malabsorption[4]

I. Entities usually associated with a diffuse severe villous abnormality and crypt hyperplasia • Celiac sprue (CS) • Other protein allergies • Lymphocytic enterocolitis
II. Entities usually associated with a variable villous abnormality and crypt hypoplasia • Kwashiorkor, malnutrition • Megaloblastic anemia • Radiation and chemotherapeutic effect
III. Entities usually associated with a nonspecific variable villous abnormality, usually not flat • Partially treated or clinically latent CS • Infection • Tropical sprue • Peptic duodenitis • Nonspecific duodenitis
IV. Entities associated with variable villous abnormalities illustrating specific diagnostic changes • Collagenous sprue • Common variable immunodeficiency • Whipple disease • Intestinal lymphoma • Parasitic infestation • Waldenström macroglobulinemia • Lymphangiectasia • Enteropathy-associated T-cell lymphoma • Abetalipoproteinemia

Table II: Differentiation between the 4 groups is illustrated in the following table.

	Category	N	Mean	Std. Deviation	'p' Value*	Significant difference from**
Age	**I**	57	32.58	17.86	0.003	II, III
	II	7	49.42	15.60		I
	III	252	40.38	15.12		I
	IV	12	38.75	12.8		
Duration of diarrhoea (days)	**I**	33	213.5	151.8	0.026	III
	II	4	123.75	123.9		
	III	132	111.69	117.41		I
	IV	5	97.00	90.53		
Hb	**I**	57	9.75	3.07	0.716	
	II	7	9.32	2.98		
	III	252	10.71	2.69		
	IV	12	10.87	3.09		
Platelets Count	**I**	57	2.1	0.90	0.794	
	II	7	1.68	0.49		
	III	252	2.24	1.06		
	IV	12	2.50	0.716		
Total Protein	**I**	57	7.09	0.69	0.523	
	II	7	6.26	1.303		
	III	252	7.20	0.74		
	IV	12	6.98	1.13		
IEL/100	**I**	57	32.84	8.98	0.000	II, III, IV
	II	7	7.57	4.15		I
	III	252	10.59	5.72		I
	IV	12	16.43	13.59		I

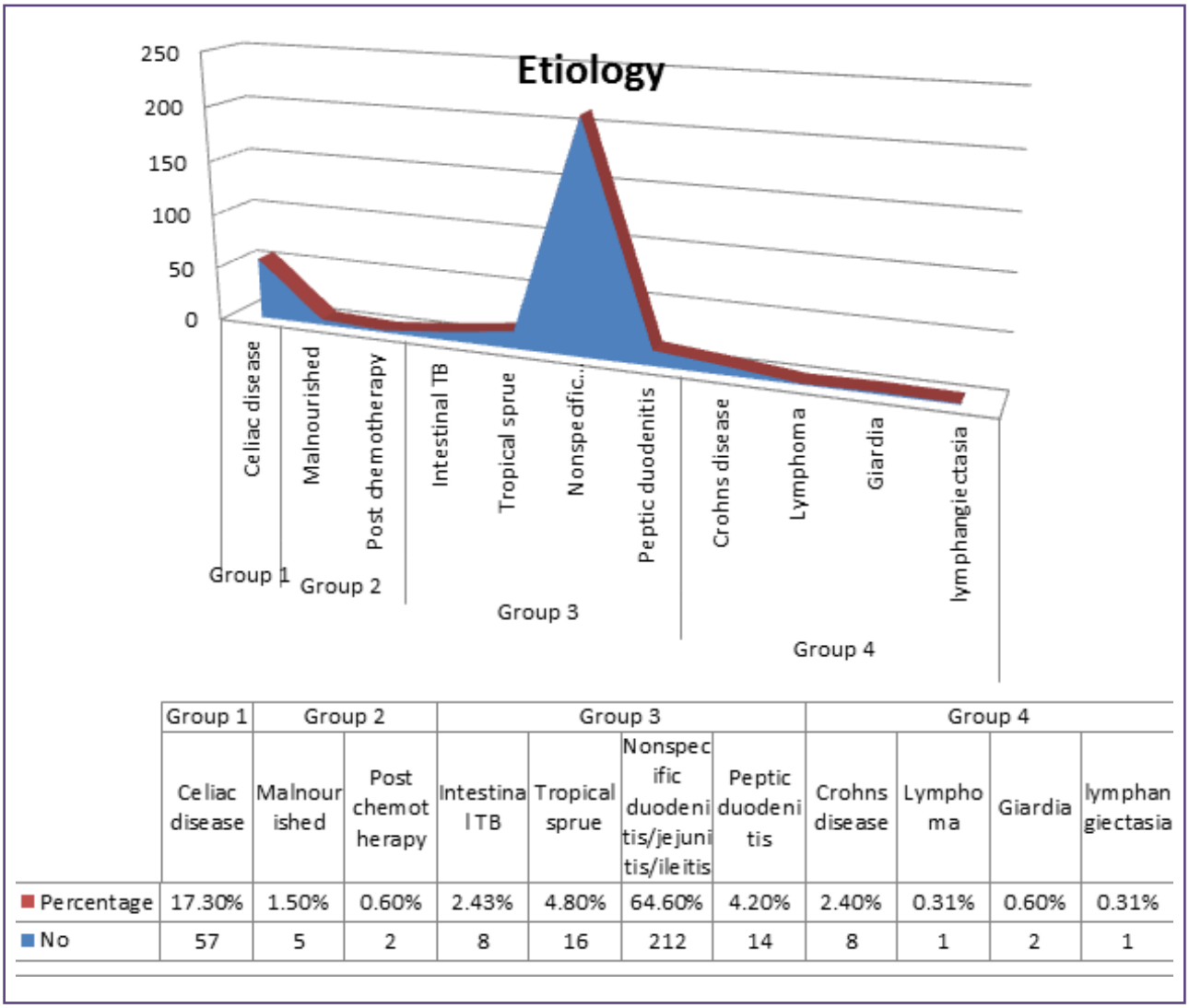
**ANOVA **Tukey HSD*

Table III: Comparison between the clinical and lab investigation of celiac disease and non specific inflammation.

Parameters		Celiac disease (n=57)	Non specific duodenitis/jejunitis/ileitis (n=212)
Age(yrs)		32.58	40.60
Male:female ratio		1: 1	1.28:1
Duration of diarrhea (days)		219.01	108.64
Clinical features	Abdominal pain Vomiting Weight loss/failure to gain weight Anemia Hypothyroidism	n =9(15.78%) n =4(7.01%) n =14(24.5%) n =24(42.1%) n=6(10.52%)	n =69(32.54%) n =12(5.66%) n=9(4.24%) n=84(39.6%) n =15(7.07%)
Investigation	Hemoglobin (gm/dL) Platelets(lacs) Total protein (g/dL)	9.75 2.11 7.03	12.42 2.29 7.21

Table I V: Comparison between the endoscopic and histological features celiac disease and non specific inflammation.

Parameters		Celiac disease (n=57)	Non-specific duodenitis/jejunitis/ileitis (n=212)
Endoscopic features	Normal folds Attenuated folds Scalloped folds Thickened folds Erythema/ulcers	11 (19.2%) 18(31.5%) 31(54.3%) 2(3.5%) 4(7.01%)	33(15.56%) 9(4.24%) 26(12.26%) 18(8.49%) 82(38.67%)
Histological features IELs/20	<6 >6	0 57 (average=32.84)	55 (25.94%) 157(74.05%)
Villous atrophy	Mild Moderate Severe	17(29.82%) 19(33.33%) 22(38.59%)	55(25.94%) 29(13.67%) 7(3.30%)
Crypt hyperplasia	normal hyperplasia	17(29.82%) 40(70.17%)	203(95.75%) 9(4.24%)



	Group 1	Group 2		Group 3				Group 4			
	Celiac disease	Malnourished	Post chemotherapy	Intestinal TB	Tropical sprue	Nonspecific duodenitis/jejunitis/ileitis	Peptic duodenitis	Crohns disease	Lymphoma	Giardia	lymphangiectasia
Percentage	17.30%	1.50%	0.60%	2.43%	4.80%	64.60%	4.20%	2.40%	0.31%	0.60%	0.31%
No	57	5	2	8	16	212	14	8	1	2	1

Fig. I: Etiology of Malabsorption.

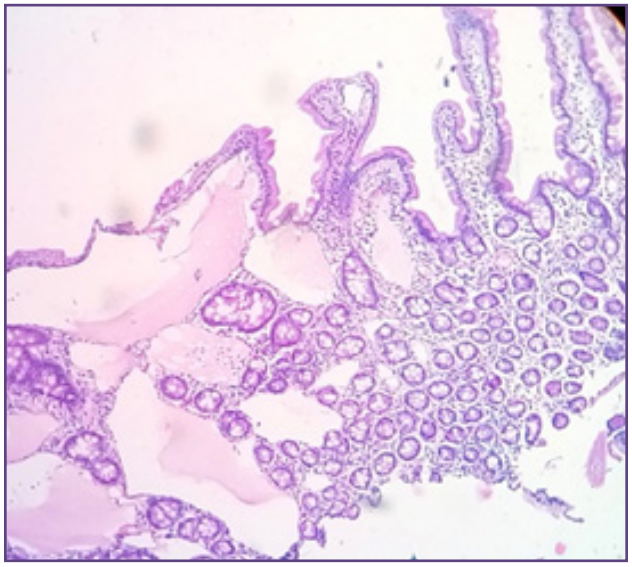


Fig. 2: Photomicrographs from a duodenal biopsy with intestinal lymphangiectasia showing distorted ,dilated villi filled with proteinaceous fluid. (Fig.2 H,andE x40).

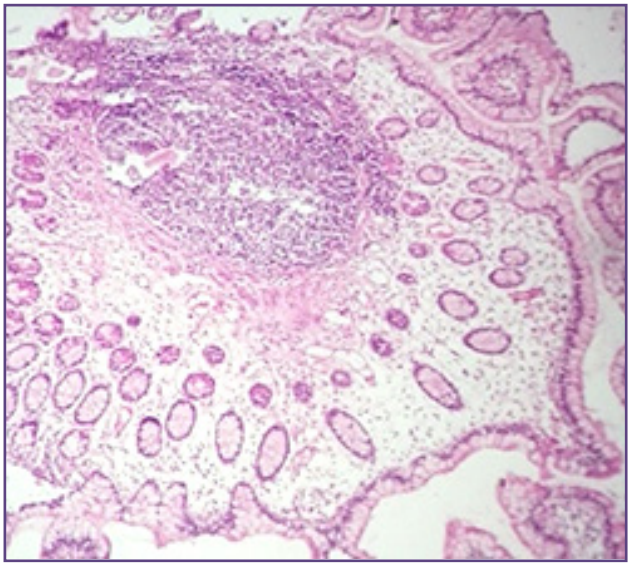


Fig. 3: Photomicrographs from a duodenal biopsy with intestinal tuberculosis showing granuloma(Fig. 3 H, and E x 40).

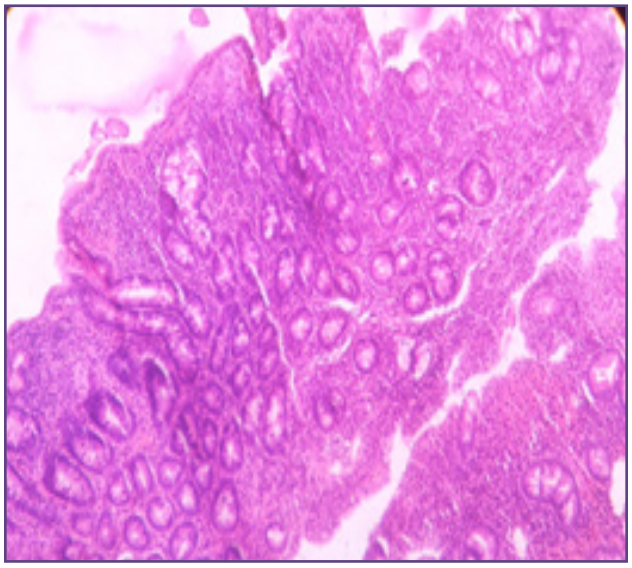


Fig. 4: Photomicrographs from a duodenal biopsy with celiac disease show markedly increased IELs, with flattening of villi and crypt hyperplasia(Fig. 4 H, and E x 40).

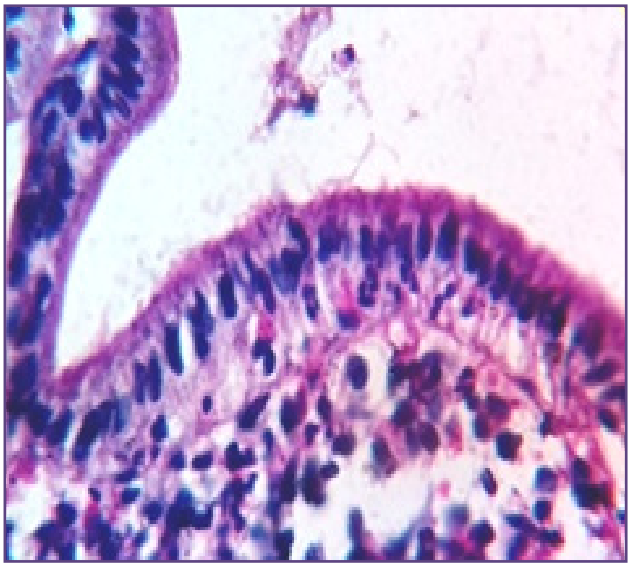


Fig. 5: Photomicrographs from a duodenal biopsy showing increased intraepithelial neutrophils in peptic duodenitis(Fig. 5 H, and E x 100).

Discussion

In the present study, most common cause of malabsorption was nonspecific inflammation followed by celiac disease. Gastrointestinal tract infections are extremely common in a developing country India because of poor hygienic conditions , may be due to chronic gastric mucosal irritation (with drugs), we tend to give a diagnosis of mild nonspecific duodenitis if we see even few lymphocytes or plasma cells in the lamina propria .

Although, our findings are also compatible with the observation of others who argued that celiac disease is common in developing countries where wheat is the major staple diet as our institution caters population of most of Rajasthan, parts of Gujarat and Harayana , where wheat is the staple diet.In most of our patients, the disease was diagnosed in adulthood. As indicated by other investigators ,most adults with celiac disease, may initially have a subclinical form of the disease and not exhibit classical symptoms of celiac

disease such as diarrhea and weight loss and may only present with subtle manifestations such as an isolated iron deficiency anemia, which may delay referral to a gastroenterologist and therefore delay the diagnosis.

However, it is surprising that specific infections such as giardiasis or tuberculosis were not more frequent. In contrast to our study, a study in Mumbai revealed celiac disease (26%) and intestinal tuberculosis (26%) were the two most common causes of Malabsorption syndrome.[5] One possible explanation for the low prevalence of ITB in this study may be due to low prevalence of malabsorption in this disorder and widespread use of anti tubercular antibiotics empirically at primary and secondary health care centres. [6] Similiarly, the low frequency of giardiasis in our series may be due to pretreatment with antibiotics before endoscopy but needs to be further investigated by conducting much larger studies to assess its true incidence and prevalence in our population.

The low prevalence of tropical sprue in our study compared to other studies may be presence of endemic and epidemic forms of disease on South India in contrast to only endemic form of tropical sprue.[6,7] Crohn's disease of small intestine can cause malabsorption due to extensive small bowel disease or resection. The emergence of crohn's disease in india has been postulated to be due to improved sanitation. Crohn's disease was reported in 9% patients in Lucknow study.[8,9] An interesting observation is the absence of IPSID as a cause of malabsorption in this study.As intestinal microbes have been postulated as trigger factors for IPSID, improved sanitation and nutrition during past decade may be responsible for absence of this disease or it may just be referral bias due to small number of patients.[6]

In conclusion, Celiac disease has emerged as a common cause of malabsorption in adults in Southern Rajasthan, where wheat is the major staple diet. We need to conduct much larger studies to assess the true incidence and prevalence of Celiac Disease in our population. In a country, where commercial gluten-free products are not easily available, it is a major challenge to maintain patients with Celiac Disease on a permanent gluten-free diet.

Consent

Written informed consent were obtained from all the patients for publication and any accompanying images.

Conflicts of Interest

The authors declare no conflict of interest.

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