

## Etiological spectrum of adults presenting with malabsorption: Experience at a tertiary centre

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### Abstract

**Introduction:** Malabsorption occurs due to different causes and the clinical presentation varies with the underlying etiology. Very few studies have been done to determine the etiological spectrum of malabsorption in northern India.

**Aim:** To assess the etiology in patients presenting with malabsorption and to study clinical, haematological, biochemical, serological, endoscopic and histological features of these patients.

**Materials and Methods:** Clinical assessment of 91 cases presenting with malabsorption complaints in the gastro OPD was done along with vitamin B12 and fecal fat estimation. Relevant haematological, serological investigations, endoscopy was done. Duodenal biopsy was taken. Data was obtained and analysed. All patients clinically presenting with malabsorption were included in the study. The patients excluded were those, who refused for endoscopy or participation in the study.

**Results:** The most common causes of malabsorption were non-specific duodenitis(42.8%), celiac disease (CD)(18.7%), tropical sprue (TS) (8.8%), giardiasis(3.3%), eosinophilic enteritis (2.2%), lymphangiectasia(1.1%), abetalipoproteinemia(1.1%) and 22% cases were normal histologically. The principal features differentiating celiac disease and tropical sprue were also noted. Patients with CD more often had anemia, scalloping of folds on endoscopy, moderate or severe villous atrophy and increased intraepithelial lymphocytes, in comparison to patients with TS.

**Conclusion:** CD is commoner than TS. Though histology is gold standard for the diagnosis of CD, TS and other intestinal mucosal diseases, correlation of histological findings with clinical, hematological, endoscopic and serological findings is important as subtle histological changes may be missed depriving the patient of proper treatment.

**Keywords:** Celiac disease, Diarrhea, Malabsorption, Tropical sprue, Villous atrophy, IELs.

### Introduction

Malabsorption syndrome is characterised by defective absorption of fat, proteins, carbohydrates and other nutrients. The causes are diverse and clinical presentation varies with underlying pathology.<sup>1</sup> Earlier tropical sprue (TS) was the commonest cause of malabsorption in India, now celiac disease (CD) appears to be becoming more common. Tropical sprue which is caused due to bacterial overgrowth was reported sporadically as well as in epidemic forms in developing countries including India.<sup>2</sup> However nowadays even in developing countries, like India, celiac disease and crohns disease appears to be increasing.<sup>3,4</sup> There is a great variation in the etiology of malabsorption syndrome in different geographical areas. There are differences in the common causes in the developed countries and the developing countries as also between the tropical and the temperate areas. In developed countries non-infectious causes like celiac disease, crohns disease and in developing countries infectious causes- tropical sprue, giardiasis are commoner. Limited studies are available determining the etiological spectrum of malabsorption in northern India. Duodenal biopsy remains the gold standard for diagnosis of CD, even though there are very specific serologic tests like anti-gluten and anti-tissue transglutaminase (anti-tTG) antibodies.<sup>5,6</sup> Correlation of

clinical, serologic, and histological features is essential for definitive diagnosis.

### Aims

The present study was done with following aims:

1. To assess the etiology in patients presenting with malabsorption.
2. To study clinical, haematological, biochemical, serological, endoscopic and histological features of these patients

### Materials and Methods

A prospective study was done over a period of 18 months, from July 2011 to January 2013. A total of 91 cases presenting with malabsorption complaints in the gastroenterology OPD of MLN medical college were enrolled in the study. All patients clinically presenting with malabsorption were included in the study. The patients excluded were those, who refused for endoscopy or participation in the study. A detailed clinical history was taken as per preset questionnaire. In the pathology department of MLN medical college tests for malabsorptions- Vit B12 Assay by IMMULITE/1000 (SIEMENS) analyser, a solid phase competitive chemiluminescent enzyme immunoassay and qualitative fecal fat estimation using sudan III along with haematological investigations and serology for anti-tissue transglutaminase (tTG) were performed.

Upper gastrointestinal endoscopy was done for all the patients and biopsies were taken from the second part of duodenum. Duodenal biopsies were fixed in 10% formal saline and processed routinely. 2-3µm thick sections were cut from paraffin embedded blocks and stained with Hematoxylin and Eosin (H&E) for histopathological examination. Histological sections were examined for any significant abnormalities, especially villous and crypt changes, intraepithelial lymphocytes, parasites or any specific lesion determining the cause of malabsorption. Intreepithelial lymphocytes (IELs) were counted per 100 epithelial cells by manual pin hole method. The data was obtained and compared statistically.

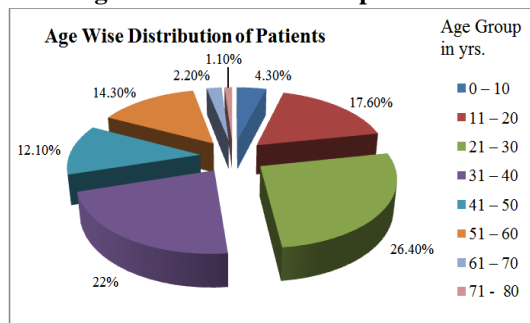
**Results**

Duodenal biopsies were taken from 95 patients. Out of 95 cases 91 were studied in detail. 4 cases were not included owing to insufficient material and very poor orientation of the sections. In present study as seen in [Chart 1] the maximum number of patients were young adults (26. 4%), in the age group 21-30 yrs. These were followed by 20 (22%) patients in age range 31-40 years. The overall age range was from 8 yrs to 76 years and the mean age of the patients was 31. 3±16 yrs. The mean age in patients with celiac disease was 30.3±17 yrs and that for tropical sprue was 35.2±7.5 yrs. As shown in Chart 2 most of the patients in present study were males (59. 3%) and females constituted 40. 6% of patients. The male: female ratio was 1. 46:1. Amongst males most patients presented in age group 21-30 years and same was in case of females. In patients with celiac disease females were more (58.8%) than males (41.1%). In present study the most common presenting symptom was bloating or abdominal distention presenting-67 patients (73.6%) followed by chronic diarrhea in 59 (64.8%) and anemia in 54(59.3%) patients. Fatigue, weakness and dyspepsia was also present in many patients. All patients with celiac disease had typical presentations, no atypical presentations were seen.

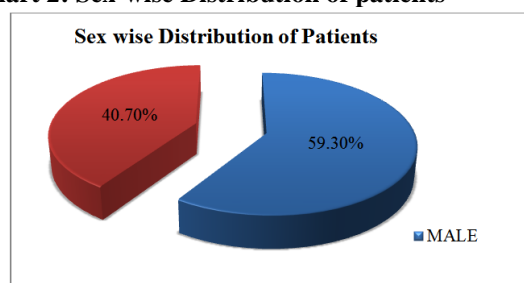
Vitamin B12 estimation, regarded as an indicator of malabsorption was done in 76 patients. The findings are seen in the Table 1. Vitamin B12 levels were

abnormal in 47 (61. 8%) patients but normal in 29 (38. 2%) patients. In celiac disease cases vitamin B12 levels were abnormally decreased in 47. 1% whereas in tropical sprue it was abnormal in 87.5% cases of cases.

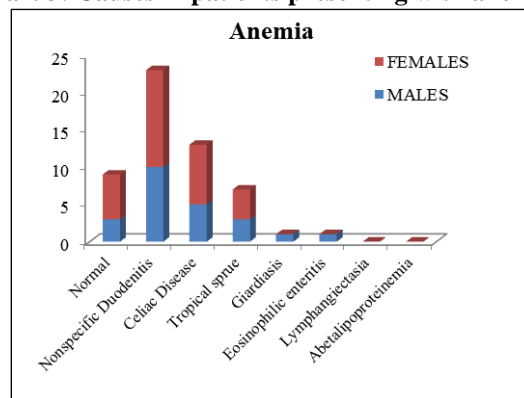
**Chart 1: Age-wise Distribution of patients**



**Chart 2: Sex-wise Distribution of patients**



**Chart 3: Causes in patients presenting with anemia**



**Table 1: Vitamin B12 estimation in patients**

Vitamin B12 estimation	Total No.	Normal	Abnormal Decreased	Range	Mean value
Celiac disease	17	9 (52.9%)	8 (47.1%)	<150-427	222.1
Tropical sprue	08	1 (12.5%)	7 (87.5%)	<150-306	181.6
Non specific duodenitis	51	19 (37.3%)	32 (62.7%)	<150-673	164.93
Total	76	29	47		

Qualitative fecal fat estimation was done in 76 cases. As seen in Table 2 in the present study it was abnormal in 63 cases (82.9%) and normal in 13 cases. (17.1%).In celiac disease fecal fat was abnormal in 16

cases (94.1%) and only 1 case (5.9%) showed normal fat excretion whereas in tropical sprue abnormality was detected in all the 8 cases (100%).

**Table 2: Qualitative fecal fat estimation in patients**

Qualitative fecal fat-	Total no.	Normal	Mild (+)	Moderate (++)	Severe (+++)
Celiac Disease	17	1 (5.8%)	7(41.2%)	7 (41.2%)	2 (11.8%)
Tropical sprue	08	-	3(37.5%)	4 (50 %)	1 (12.5%)
Non specific Duodenitis	51	12 (23.5%)	17 (33.3%)	14 (45.1%)	8 (15.7%)
Total	76	13	27	25	11

During endoscopy duodenum appeared normal in most of the cases. In CD attenuated folds were seen in 76.5%, scalloping in 29.4% cases, nodularity in 23.5% and ulcerations in 35.3% cases. Compared to CD, in TS attenuated folds were present in only 12.5% and scalloping, nodularity or ulceration was not seen.

Anemia was a common clinical presentation in the present study seen in about 54(59.3%) patients. 13(76.5%) patients of celiac disease and seven (87.5%) patients of tropical sprue had anemia. [Chart 3] The mean haemoglobin was 7.3 and mean MCV was 75.3 in celiac disease. In tropical sprue mean haemoglobin were 7 and the mean MCV was 111.3.

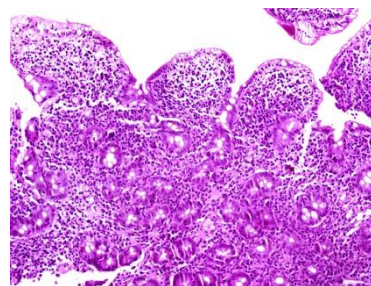
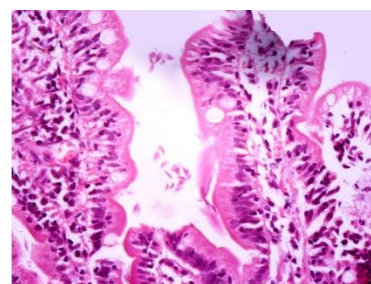
As seen in Table 3 On histological examination of the 91 duodenal biopsies 21 were normal and abnormalities were noted in 70 cases. Villi were tall and slender and the villous: crypt ratio was more than one. Lamina propria showed few chronic inflammatory cells consisting of lymphocytes and plasma cells. Intraepithelial lymphocytes were seen in the epithelial lining. 70 duodenal biopsies showed evidence of histological abnormalities. Diagnoses were made paying special attention to the villous architecture, the villous: crypt ratio, the intraepithelial lymphocyte count, inflammation in lamina propria.

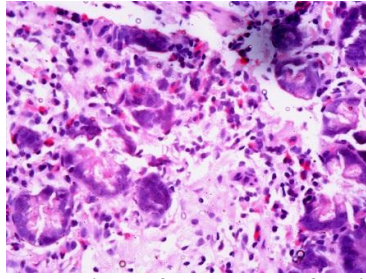
**Table 3: Histological diagnosis of duodenal biopsies**

S. No.	Histological diagnosis	No of patients	%
1	Nonspecific	45	49.
2	Normal	21	23.
3	Celiac Disease	10	11
4	Tropical Sprue	08	8.8
5	Giardiasis	03	3.3
6	Eosinophilic	02	2.2
7	Lymphangiectasia	01	1.1
8	Abetalipoproteinemia	01	1.1
	Total	91	100

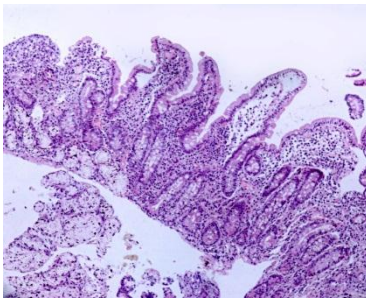
Out of these 70 cases 45 were diagnosed as nonspecific duodenitis, followed by celiac disease (ten cases) and tropical sprue (eight cases)[Fig. 1][Fig. 2]. Other cases were – giardiasis(three), eosinophilic enteritis (two), lymphangiectasia (one) and abetalipoproteinemia(one)[Fig. 3][Fig. 4.] On histological examination. Complete villous atrophy was seen exclusively in celiac disease while in tropical sprue maximum patients showed grade II villous

atrophy. IELs were increased in cases of celiac sprue as compared to patients with diagnosis of celiac sprue or non specific duodenitis. Present study showed statistical significance in comparing IELs in the villi and the crypt in CD and TS ( $p < 0.001$ ). Final diagnosis was made on the basis of histological diagnosis correlated with serological findings and response to treatment. Serology for Ttg showed that all histologically diagnosed celiac disease were seropositive. Also six cases diagnosed as non specific duodenitis and one case which appeared normal histologically showed positivity for tTg. These seven cases were started on gluten free diet. They showed improvement with amelioration of symptoms. so, these seven cases were diagnosed as celiac disease. Finally 17 cases were diagnosed as celiac disease. Final diagnosis remained non specific duodenitis in 39 cases. These were negative on serology. The eight cases of tropical sprue diagnosed histologically were treated with antibiotics, tetracycline and responded well to treatment confirming the diagnosis. Besides these the final diagnosis in all other cases was same as histological diagnosis.

**Fig 1: Duodenal biopsy (D2) from a case of celiac disease showing almost flattened villi and increased inflammation in lamina propria and increased IELs [H&E ×40]****Fig 2: Duodenal biopsy from a case of Giardiasis showing trophozoites of Giardia lamblia. [H&E ×400]**



**Fig 3: Duodenal biopsy from a case of eosinophilic enteritis showing surface ulceration, marked inflammation in lamina propria with predominance of eosinophils [H&E ×100]**



**Fig 4: Duodenal biopsy from a case of tropical sprue showing partial flattening of villi and inflammatory infiltrate in lamina propria [H&E ×40]**

### Discussion

The spectrum of malabsorption in India was assessed by Dutta et al.<sup>7</sup> Out of 124 pts in nine year period, tropical sprue was the commonest etiology (29%) followed by celiac and crohn's disease (15.3% each). Other important etiologies included parasitic infestations (9.7%) and immune deficiency disorders (5.6%). Intestinal tuberculosis was seen in only 2.4% patients. A change in etiological spectrum of malabsorption was seen. Celiac disease and inflammatory bowel disorders were emerging as important causes and Immuno Proliferative Small Intestinal Disease (IPSID) and intestinal tuberculosis were on the decline. Tropical sprue however was the commonest cause as in the past. In the study by Yadav et al 94 consecutive patients (age >12 years) with chronic diarrhea and malabsorption syndrome were included.<sup>8</sup> Celiac disease (65%) was the most common cause of malabsorption followed by tropical sprue (22%). Other conditions were cyclosporinosis (three), Crohn's disease (two), common variable immunodeficiency (two), lymphangiectasia (one), William's syndrome (one), and idiopathic malabsorption (three). A study in northern India included 99 patients and found tropical sprue was most common cause of malabsorption (39%), followed by celiac disease and crohns disease (9% each), giardiasis (8%) lymphangiectasia (1%), intestinal tuberculosis (4%).<sup>9</sup> However in 15% cases no obvious cause was determined, i.e. idiopathic. The present study showed

celiac disease is more common than tropical sprue which correlated with finding of Yadav et al however study of Dutta et al showed a higher prevalence of tropical sprue, the decrease in cases of tropical sprue as also seen in the present study may be due to various reasons. The possibilities are improvement in the socioeconomic status, better sanitation and hygiene, as well as irrational use of antibiotics readily available over the counter without medical prescription or antibiotic treatment for any other infection there was no significant difference in the mean age of presentation in celiac disease, tropical sprue similar to the study by Ranjan et al. In present study the most common causes were non specific duodenitis (42.8%), celiac disease (18.7%) tropical sprue (8.8%), giardiasis (3.3%) eosinophilic enteritis (2.2%), lymphangiectasia (1.1%) and abetalipoproteinemia (1.1%), 22% cases were normal histologically. It is still controversial what are the most common causes of malabsorption in India and what are factors causing the difference. An apparent regional variation of occurrence in India has been seen, possibly due to differences in genetic predisposition, differences in consumption of wheat or both.<sup>10</sup> The decrease in cases of tropical sprue also seen in the present study may be due to various reasons. The possibilities are improvement in the socioeconomic status, better sanitation and hygiene, as well as irrational use of antibiotics readily available over the counter without medical prescription or antibiotic treatment for any other infection.<sup>11</sup> As tropical sprue readily responds to antibiotics, it may get treated in many cases without even being diagnosed. Varying prevalence of celiac disease has been reported from different countries. In India the prevalence varies from 9% to 18% including the present study. Yadav et al reported it as 65%. They attributed this high prevalence to underdiagnosis of celiac disease and to missing of cases due to atypical presentation. In present study the patients were selected on the basis of clinical features, where malabsorption was suspected even if features were mild because the symptoms were persistent for months. This was done to avoid missing of cases in which the cause of malabsorption could be determined. Henceforth suspicion of intestinal mucosal lesion was raised. In present study the mean age of all the patients was  $31.3 \pm 16$  yrs. The mean age in celiac disease was  $30.3 \pm 17$  yrs and that for tropical sprue was  $35.2 \pm 7.5$  yrs the maximum number of patients of celiac disease were young adults as also seen by Yadav et al. Most of them were females (M:F=1:1.4). There was no significant difference in the mean age of presentation in celiac disease, tropical sprue similar to the study by Ranjan et al where mean age in all pt was  $34.6 \pm 9.1$ , in tropical spue  $33.6 \pm 9.8$ . The M:F ratio were similar in these study groups. In another study by Kalhan et al mean age of presentation of celiac disease was  $26.5 \pm 10.3$  years and the predominance of females was seen but was not significant.<sup>8,9,12</sup> The present study also



showed female predominance in celiac disease however it was not statistically significant. The study by Cev et al showed celiac disease was more frequently diagnosed in females (75%) in fourth and fifth decades of life. Although there is no gender preference, celiac disease is detected two-to-threefold more commonly in women, perhaps because monthly menstrual bleeding increases the demand for iron and vitamins and accentuates the effects of impaired absorption.

Previous studies reported diarrhea as the most common clinical feature in 95% and 41.66% cases respectively. In present study most common presenting symptom was bloating or abdominal distention present in 67 patients (73.6%) followed by chronic diarrhea 64.8%. In 9.9 % patients alternating diarrhea and constipation was observed. Taking both these groups together diarrhea was most common presentation. In present study anemia was present in overall 59.3% patients, slightly more than study by Cev et al (50%).<sup>9,13</sup> Thus presence of anemia in patients with chronic diarrhea should be evaluated. 76.5% patients of celiac disease and 87.5% patients of tropical sprue had anemia. Anemia was more common in tropical sprue than celiac and was statistically significant ( $p < 0.05$ ). Iron deficiency was seen in most cases of celiac disease (mean hgb 7.3gm% and mean MCV 75.3fl) whereas in tropical sprue megaloblastic anemia (mean hgb 7 gm% and mean MCV 111.3fl) was more frequent. This proved to be statistically significant. Similar were the finding of Yadav et al. In study by Ranjan et al in cases of tropical sprue mean hgb was  $9.6 \pm 2$  and overall hgb was  $9.8 \pm 1.9$ . Complete villous atrophy was seen exclusively in celiac disease while in tropical sprue maximum patients showed grade two villous atrophy. Three counts of IEL/100 epithelial cells done in biopsies showing subjective increased IELs helped to recognize latent coeliac disease with normal villi.<sup>14</sup> Along with histology serology plays an important role. In present study six cases originally diagnosed as non specific duodenitis proved to be celiac disease when serology for tTG was positive and patients were reevaluated and tried on gluten free diet, dramatic positive response was seen. Even one case with normal villi was finally diagnosed as celiac disease. In a study by Ucardagi et al control subject (0.8%) had histopathologic findings of celiac disease. All subjects positive for anti-tTG IgA had histopathological findings of celiac disease on duodenal biopsy.<sup>15</sup> In present study also all patients with histological diagnosis of celiac disease had serology for anti-tTg positivity. One of our patients with normal histology was diagnosed as celiac disease on serology who responded well to gluten free diet. Celiac disease may be missed on histology in poorly oriented biopsies or when the cut off for IELs is high, especially Marsh grade I celiac disease. Ideally, celiac serology should be performed prior to biopsy, however in practice this is often not seen and is done on suggestion of the pathologist.<sup>16</sup> Hence, the

pathologist may not have any suggestive clinical data and subtle changes in celiac disease may be missed.

### Conclusion

CD is commoner than TS. Though histology is gold standard for the diagnosis of CD, TS and other intestinal mucosal diseases; correlation of histological findings with clinical hematological, endoscopic and serological findings is important as subtle histological changes may be missed depriving the patient of proper treatment.

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**Conflicts of Interest:** None

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