Original Research Article

Recent etiologies of Malabsorption syndrome among adults and features differentiating celiac disease and tropical malabsorption

Akula Sanjeevaiah[1], Akula Sushmitha[2*], Thota Srikanth[3]

[1]CSS Gen Medicine, [3]MD Gen Medicine, Dist. Head Quarter Hospital, Warangal Rural, India
[2]Post graduate in Internal Medicine, NIMS, Hyderabad, India
[*]Corresponding author email: **Akulasanjeev2013@gmail.com**

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Abstract

Introduction: There is a constant change in the order of etiologies causing Malabsorption syndromes in India. Establishing the etiology of this challenging clinical disorder requires judicious use of a wide array of tests. Implementation of preventive health measures and improved sanitation may have changed the etiology of mal absorption syndrome.

Aim: This study was aimed to document the recent etiologies of malabsorption syndromes and also to compare the features that differentiate tropical sprue from celiac disease, the recent two most common etiologies of mal absorption seen at our centre.

Materials and methods: Patients seen at our centre with malabsorption syndromes from February 2016 to November 2018 were included in this study. The etiological, clinical and investigation details were recorded on uniform structured data forms. The data obtained was statistically analyzed.

Results: Out of the 300 patients screened, 200 patients were included in the study; the other 100 patients were not included as they did not fit in to the inclusion criteria for malabsorption syndrome. Of these 200, 22 (11%) patients were in the age group between 13-19 years. Tropical malabsorption (n=82) was the common cause of MAS followed by celiac disease (n=42). 35 of 42 patients (83.3%) with celiac disease, who underwent test for anti-endomysial antibody, had positive result followed by giardiasis and other diseases. Of the remaining seven patients, four had low level of serum IgA, one had anti-tTG antibody and others had anti-gliadin antibody in serum. Two patients with strongyloidosis, Two patients with Chron's and one patient with IPSID died. Frequency of recurrence

after successful treatment was comparable among patients with celiac disease and tropical malaabsorption (two patients each) during a follow up period of 13.7 ± 16.1 and 14.7 ± 10.5 months, respectively.

Conclusion: In the present study, tropical malabsorption and celiac disease were the most common causes of mal-absorption syndrome followed by giardiasis, AIDS and tuberculosis.

Key words

Malabsorption Syndrome, Giardiasis, Celiac Disease.

Introduction

Malabsorption syndrome (MAS) is a common condition in Medical practice in tropics including India [1]. The spectrum of mal absorption syndrome differs in different geographical areas. Non infectious diseases like celiac disease and crohn's disease are common in developed countries like India whereas infectious diseases like intestinal tuberculosis, tropical sprue, parasitic infections, and primary immunodeficiency syndromes are common in developing countries. With socio-economic improvement and sanitary conditions and increasing use of antibiotics the frequency of tropical malabsorption may have declined in the tropical countries in the present time. Improvements in living standard and enhanced hygienic condition have possibly led to decline in number of patients with MAS. On the other hand, Celiac disease (CD), is being recognized globally and a recent meta-analysis on global prevalence of CD showed that 0.68% of global population has CD. While the over- all prevalence of CD varies from less than 1% to > 5% in different regions of the world, in India, its prevalence equates to that of the western Caucasian population, which is about 0.6–1% [2]. In India, Celiac disease (CD) was once thought to be uncommon, is being reported frequently as a cause of MAS among children and adults [3, 4]. India has seen the emergence of celiac disease and inflammatory bowel disease, since the last decades. Socioeconomic health development and improvement and sanitation might have reduced the chronic infective diarrhea incidence and tropical sprue and changed the mal-absorption spectrum. This study aimed to assess the spectrum of MAS among patients and features that may help to differentiate TM and CD among them.

This study was thus aimed to assess the spectrum of MAS among Indian adults, and features that may help to differentiate TM and celiac disease among them.

Materials and methods

All patients with malabsorption syndrome attending General Medicine Department at our centre during 3 year period were included in our study. All the patients were screened and evaluated with a standard protocol, which was approved by institutional ethical committee. Those with diarrhea of more than 1 month duration and abnormality in at least two of the following tests: i) Urine or blood xylose absorption test, ii), quantitative fecal fat measurement or fecal sudan stain, iii) duodenal biopsy were included in the study. Inclusion criteria included in at least two of three tests (urine D-xylose 7g/day or fecal Sudan stain >10 droplet/high power field), patients with abnormal results and any degree of villous atrophy on duodenal histology], clinical evidence supporting a definite specific cause of MAS and patients with abnormal results on one of the three tests. According to the standard protocol, to identify the etiology of malabsorption syndrome, following investigations were done which were stool microscopy with various staining methods, hemogram, blood biochemistry including routine investigations, folate and vit B12 levels, serological tests (human immunodeficiency virus Enzyme immunoassay), anti-endomysial antibody test indirect immunofluorescence assay, quantitative estimation of immunoglobulins

(IgA, IgG and IgM) levels in serum, small bowel barium series, endoscopic duodenal or jejunal biopsies, which was interpreted by an experienced pathologist using a standard grading system, glucose hydrogen breath test (using 100 g glucose to diagnose SIBO). Abdominal ultrasonography, bone marrow biopsy, and colonoscopy were done at required times on clinical grounds. Tests done to assess absorption: During a 5 h period following ingestion of 5 g of D-xylose, using a colorimetric method, D-xylose test was performed to estimate the amount of D-xylose excreted in urine. Excretion of < 1.0 g D-xylose was considered abnormal. Fecal fat was estimated by after a three day fat load (75 g/day). During the next three days, daily stool collection was done, during which fat loading was continued. Mean daily stool weight and mean daily fat excretion was calculated. Fecal fat excretion >7 g/day was considered abnormal. Faecal fat was also tested by microscopic examination of the spot stool specimen stained with Sudan III stain. Fecal Sudan >10 droplets per high power field was considered as abnormal. For all the patients, nutritional and supportive measures were taken in common and specific treatment included the gluten-free diet, antibiotics, nitroimidazole, azathioprine and/or corticosteroids, ATT, medium chain triglycerides, highly active anti-retroviral therapy, albendazole, tetracycline and anti-malignant chemotherapy as indicated for CD, SIBO, giardiasis, Crohn's disease, tuberculosis, lymphangiectasia, AIDS, strongyloidiasis and IPSID, respectively. Treatment with tetracycline (500 mg thrice daily for one month and 500 mg twice daily for another one month) and folic acid (10 mg daily for at least 6 month) for patients with malabsorption. Treatment with ciprofloxacin or norfloxacin or rifaximin was given in non-responsive patients with tropical malabsorption and SIBO. The following parameters were evaluated for response to treatment during follow up visits, namely stool frequency reduction, decrease in steatorrhea, increase in body weight, improvement in hemoglobin concentration and serum albumin, normalization of urinary excretion of D-xylose, and duodenal histology. Statistical Analysis was done by using Excel software and Mean±SD, percentages were analyzed with P-values.

Results

Out of the 300 patients screened, 200 patients were included in the study; the other 100 patients were not included as they did not fit in to the inclusion criteria for malabsorption syndrome. Of these 200, 22 (11%) patients were in the age group between 13-19 years.

Table - 1 shows that urinary excretion of D-xylose, performed in 180/200 (90%) patients, was 0.68±0.55 g/5h. It was abnormal in 167 of 180 (92.7%) patients with MAS. The mean fecal fat excretion, estimated in 140/200 (70%) patients, was 8.1 ± 3.9 g/day. It was abnormal in 99 of 140 (70.7%) patients. The median fecal fat excretion by Sudan stain, evaluated in 155 of 200 (77.5%) patients, was 19 (range 4 - 50) droplets/ HPF. It was abnormal in 139 of 155 (89.7%) patients.

Table - 1: Results of investigations for mucosal malabsorption.

Investigations	Number of Patients (%)	Average Value
Urine D-Xylose	180/200 (90%)	0.68±0.55 g/5h
Faecal Fat	140/200 (70%)	8.1±3.9 g/day
Faecal Sudan Stain	155/200 (77.5%)	19 droplets/HPF

Table - 2 shows that duodenal biopsy was obtained in 170 (85%) patients with MAS; 18 (10%) had subtotal villous atrophy, 40 (23.5%) had partial villous atrophy, 38 (22.3%) had blunting of villi and two patients had normal villi. 194 (97%) had increased mononuclear infiltrate and 108 (54%) had increased intraepithelial lymphocytes.

Table - 2: Results of histopathological examination of duodenal biopsy.

Investigations	Number of Patients	Percentage
Subtotal Villous Atrophy	18	10%
Partial Villous Atrophy	40	23.5%
Blunting of villi	38	22.3%
Normal Villi	2	1.1%

Table - 3: Aetiology of mal-absorption syndrome.

Aetiology of MAS	Number of Patients	Percentage
Giardiasis	10	5%
Intestinal Tuberculosis	6	3%
Strongyloidiasis	4	2%
AIDS	15	7.5%
IPSID	4	2%
Amyloidisis	4	2%
Crohn's disease	5	2.5%
Tropical Malabsorption	82	41%
Celiac Disease	42	21%

Table - 3 shows that of the 10 (5%) patients with giardiasis (median age 42 year, range 12-55 year, 7 (70%) male), 3, 4 and 3 were diagnosed using stool microscopy, histopathology and both tests, respectively. Two patients had very low level of serum IgA. All the patients responded to treatment with a nitroimidazole. Of the six (3%) patients with intestinal tuberculosis, (median age 40 year, range 23-68 year, 5 (83 %) male), 4 patients had acid fast bacilli (AFB) on microscopic examination of smear, one grew AFB on the culture and showed its DNA by polymerase chain reaction. 3 other patients had features of ileo-cecal tuberculosis on small bowel barium series including ileo-colic fistula in one and jejunal stricture in another, multiple abdominal lymphadenopathy on computerized tomography scan and positive Mantoux test. All the patients responded to ATT. Of the 4 (2%) patients with strongyloidiasis (median age 30 year, range 18-70 year, 3 (75%) male), larvae of strongyloides parasite were detected on microscopic examination of stool or histopathological examination of duodenal biopsy in two each. Both of them were receiving corticosteroids and one had hypogammaglobulinemia. Peripheral blood eosinophilia was absent in three patients. Two patients died of septicemia. One patient with AIDS also had larvae of strongyloides on stool microscopy. Fifteen (7.5%) patients (median age 36 year, range 30-58 year) had AIDS. Patients with AIDS were more often male patients than those with MAS due to other causes (12/14 (85.7%) vs. 130/190 (68.4%), $P<0.03$). Patients with AIDS (n=15) and intestinal lymphangiectasia (n=3) had lower level of absolute lymphocyte count than MAS due to other causes Stool microscopy revealed larvae of strongyloides in 2, *Isospora belli* cyst in 2, eggs of ascaris in three, both *Hymenolepis nana* and Cryptosporidium in one. Three patients had history of sexual promiscuity, two had undergone prior surgery and two had history of blood transfusion. Three patients with intestinal lymphangiectasia were diagnosed on duodenal biopsy and were responded to treatment with median chain triglycerides. Four (2%) patients (age 34 year, range 28-40 year, all male) were diagnosed as IPSID on duodenal biopsy. All patients presented with chronic small bowel diarrhoea and weight loss. One patient had been treated with ATT in the past by community physician. One patient had a mass in the right iliac fossa and one had digital clubbing. Two patients had SIBO on glucose hydrogen breath

test and one had Giardia on stool microscopy. Three patients had increased level of serum alkaline phosphatase (median 128 (range 61 to 418 U/l)). Two patients were successfully treated with tetracycline alone for early disease. Remaining one died of explosive diarrhea and shock while receiving anti-cancer chemotherapy .Of the 200 patients with MAS, four (2%) (median age 48 year, range 24 to 60 year, four male) had presence of amyloid on rectal biopsy (n=2), duodenal biopsy (n=1) or abdominal fat pad aspirate (n=1) using Congo red staining. Of the 200 patients with MAS, five (2.5%) (median age 36 year (range 22 to 53 year), 4 male) had Crohn's disease. Two of them had ileo-colic fistula. Two patients had been treated with ATT in the past. One patient had SIBO on GHBT. Four patients responded to treatment and one died of sepsis. Tropical malabsorption (n=82) was the common cause of MAS followed by celiac disease (n=42). 35 of 42 patients (83.3%) with celiac disease, who underwent test for anti-endomysial antibody, had positive result. Of the remaining seven patients, four had low level of serum IgA, one had anti-tTG antibody and others had anti-gliadin antibody in serum. Two patients with strongyloidosis, two patients with Chron's and one patient with IPSID died. Frequency of recurrence after successful treatment was comparable among patients with celiac disease and tropical malabsorption (two patients each) during a follow up period of 13.7 ± 16.1 and 14.7 ± 10.5 months, respectively.

Discussion

Chronic small bowel diarrhea with malabsorption poses significant impairment to health related quality of life in India. India is apparently witnessing a paradigm shift from the infectious causes to non-infectious causes of malabsorption as the sanitation and hygienic conditions are improving. This fact was reported recently by Yadav, et al. who concluded that the celiac disease was the most common cause of chronic diarrhea with malabsorption in northern India [3]. But the rest of the country seems to still be grappling with tropical sprue. Studies from Ghoshal, et al. [5], from Dutta, et al. [6] from south India reported that celiac disease is a rapidly emerging disease but tropical sprue is still the leader [4, 5]. Our study shows that tropical malabsorption and celiac disease dominates the spectrum. In a study done by Das K, et al. [7]; age at onset and duration of symptoms (182 patients, 117 male) were 34.5 (+/-13.6; 7-73) years and 3.0 (+/-5.8; 0.1-36) years, respectively. Diarrhea (68%), abdominal pain (62%), and weight loss (57%) were common. The common intestinal complications were occult (27%) and overt (40%) gastrointestinal bleeding and obstruction (28%). There were 141 (78%) and 41 (22%) with definite and probable Crohn's disease respectively. Of 147 (81%) available histopathology specimens (endoscopic biopsy in 110; 75%), 31 (21%) had granuloma. Seventy-one out of 166 (43%) had received anti-tuberculosis therapy in the past. Results from the Montreal classification were as follows: age at onset, A1:A2:A3 6%:64%:30%; location of disease, L1:L2:L3:L4 32%:41%:23%:4%, and disease behavior, B1:B2:B3 51%:24%:25%. Twenty-six (15%) and 31 (17%) patients had upper gastrointestinal and perianal modifiers. The drugs used were: aminosalicylates (128, 70%), steroids (76, 42%), azathioprine (53, 29%), methotrexate (4, 2%), and salazopyrine (14, 8%). Sixty-six (36%) patients underwent surgical treatment. Nirav Pipaliya, et al. [8]; showed that the most common etiology was tropical sprue (n=98, 48.3%) followed by parasitic infections (n=25, 12.3%) and tuberculosis (n=22, 10.8%). Other causes were immunodeficiency (n=15, 7.3%; 12 with human immunodeficiency virus and 3 with hypogammaglobulinemia), celiac disease (n=11, 5.4%), Crohn's disease (n=11, 5.4%), small intestinal bacterial overgrowth (n=11, 5.4%), hyperthyroidism (n=4, 1.9%), diabetic diarrhea (n=4, 1.9%), systemic lupus erythematosus (n=3, 1.4%), metastatic carcinoid (n=1, 0.5%) and Burkitt's lymphoma (n=1, 0.5%). On multivariate analysis, features that best differentiated tropical sprue from parasitic infections were larger stool volume (P=0.009), severe weight loss (P=0.02),

knuckle hyperpigmentation (P=0.008), low serum B12 levels (P=0.05), high mean corpuscular volume (P=0.003), reduced height or scalloping of the duodenal folds on endoscopy (P=0.003) and villous atrophy on histology (P=0.04). Presence of upper gastrointestinal (GI) symptoms like bloating, nausea and vomiting predicted parasitic infections (P=0.01). Pragya Sharma [9] showed that between the patients with CD and TS, there was no difference in the prevalence and duration of chronic diarrhea, abdominal distension, weight loss, extent of abnormal fecal fat content, and density of intestinal inflammation. The following features were more common in CD: shortstature, vomiting/ dyspepsia, endoscopic scalloping/ attenuation of duodenal folds, histological high modified Marsh changes, crescendo type of IELosis, surface epithelial denudation, surface mucosal flattening, thickening of subepithelial basement membrane and celiac sero positivity; while those in TS include anemia, abnormal urinary D-xylose test, endoscopic either normal duodenal folds or mild attenuation, histologically decrescendo type of IELosis, low modified Marsh changes, patchy mucosal changes, and mucosal eosinophilia. Ramakrishna BS, et al.[10] showed that malabsorption is an important clinical problem both in visitors to the tropics and in native residents of tropical countries. Infections of the small intestine are the most important cause of tropical malabsorption. Protozoal infections cause malabsorption in immunocompetent hosts, but do so more commonly in the setting of immune deficiency. Helminth infections occasionally cause malabsorption or protein-losing enteropathy. Intestinal tuberculosis, chronic pancreatitis and small-bowel bacterial overgrowth are important causes of tropical malabsorption. In recent years, inflammatory bowel disease and coeliac disease have become major causes of malabsorption in the tropics. Sporadic tropical sprue is still an important cause of malabsorption in adults and in children in South Asia. Investigations to exclude specific infective, immunological or inflammatory causes are important before considering tropical sprue as a diagnosis. Tropical malabsorption and celiac disease are common causes of MAS among Indian adults in the present study. Next common etiology was giardiasis, acquired immunodeficiency syndrome and tuberculosis. Other rare causes were Crohn's disease SIBO, hypogammaglobulinemia, IPSID, amyloidosis and intestinal lymphangiectasia. In 5% cases, the etiology remained unknown.

Conclusion

In the present study, tropical malabsorption and celiac disease were the most common causes of mal-absorption syndrome followed by giardiasis, AIDS and tuberculosis (Should not be same as abstract conclusion).

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