Etiological spectrum of sporadic malabsorption syndrome in northern Indian adults at a tertiary hospital

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Background: The etiology of malabsorption syndrome (MAS) may differ in different geographical regions. Limited data are available on the etiological spectrum of MAS among Indian adults. Methods: Ninety-nine consecutive adult patients with MAS (urine d-xylene <1 g/5 g/5 h with or without increased fecal fat (>7 g/24 h) were evaluated for cause of MAS using standard criteria. Past medical records were examined to know the nature of treatment received. Results: The etiology of MAS was: tropical sprue 39, celiac disease 9, Crohn's disease 9, giardiasis 8, small intestinal bacterial overgrowth in absence of another cause of MAS 8, panhypogammaglobulinemia 2 (one with strongyloidiasis), intestinal lymphangiectasia 1, intestinal tuberculosis 4, idiopathic 14, acquired immunodeficiency syndrome 2, and amyloidosis 2. Twenty-eight patients had received anti-tubercular treatment earlier. Conclusions: Tropical sprue, celiac disease and Crohn's disease are common causes of MAS in adults. Inappropriate anti-tubercular treatment is common in them and needs to be discouraged. [Indian J Gastroenterol 2004;23:94-98]

Key words: Celiac disease, Crohn's disease, small bowel diarrhea, tropical sprue

The etiology of malabsorption syndrome (MAS) may differ in different geographical regions. In developed countries, non-infectious causes like celiac disease and Crohn's disease are common. In contrast, infectious diseases are likely to be more common in developing countries like India. Tropical sprue (TS), a disease presumed to be associated with small intestinal bacterial contamination, was reported in sporadic and epidemic forms from India in the past. However, it is now believed that, with improvement in socioeconomic status and sanitation, TS is becoming infrequent in India. Also, in recent years, celiac disease and Crohn's disease have been increasingly reported in children and adults from India. Reports on the frequency of immunoproliferative small intestinal disease (IPSID) in India are conflicting. Some authors believe it to be common, though without much evidence to support this.

No prospective study on the etiological spectrum of MAS among adults has been reported from India, and hence this report. Data of small bowel bacterial flora and its antibiotic sensitivity pattern and oro-cecal transit time of 50 and 13 of these patients have been reported previously. One patient with strongyloidiasis included in this study has also been reported previously.

Methods

Consecutive adult patients with MAS referred to the Luminal Gastroenterology Clinic at our institution between August 2000 and February 2002 were included. Inclusion criteria were presence of any two of the following: (a) chronic large-volume diarrhea, and (b) abnormal urinary d-xylene (<1 g/5 g/5 h), and/or (c) abnormal fecal fat (>7 g/24 h).

Patients were investigated for etiology and systemic effects of MAS according to a standard protocol (Fig). Serological tests included antibodies to human immunodeficiency virus (enzyme immunoassay, XIV Chek, Qualigens Diagnostics, Bangalore, and Comb AIDS, Span Diagnostics, Surat), and endomyxum (indirect immunofluorescence assay; Binding Site, Birmingham, England), abnormal alpha heavy chain, and quantitative estimation of MAS among adults has been reported from India, and hence this report. Data of small bowel bacterial flora and its antibiotic sensitivity pattern and oro-cecal transit time of 50 and 13 of these patients have been reported previously. One patient with strongyloidiasis included in this study has also been reported previously.

![Diagram of protocol for work-up of patients with malabsorption syndrome](image)

Fig: Protocol of work-up of patients with malabsorption syndrome (*jejunal aspirate culture was performed in 50 patients; **tests for abnormal alpha heavy chain was performed in 38 patients)
of serum immunoglobulins (IgA, IgG and IgM). Abdominal ultrasonography (in 74 patients), bone marrow examination (8 patients), and colonoscopy (in 7 with Crohn's disease, 2 with intestinal tuberculosis, 2 with HIV infection, and 2 idiopathic) were done when deemed necessary. Bacterial culture and colony count of jejunal aspirate (in 50 patients), and glucose hydrogen breath test (using 100 g glucose; Lactoscreen H₂ breath tester, HoeckLoos, Amsterdam, Netherlands) were done using previously described techniques¹² to diagnose small intestinal bacterial overgrowth (SIBO). In patients with SIBO without another cause of MAS, conditions predisposing to SIBO were searched for by history and barium studies of small bowel and colon. In patients in whom no structural defect was identified and who had a systemic disease that can affect small intestinal motility, antroduodenal manometry was done using a water perfusion manometry system (RedTech, Calabasas, CA, USA). If no migratory motor complex (MMC) was observed during a fasting phase recording, an attempt was made to induce one using an intravenous injection of 50 μg octreotide since MMC may at times be absent in healthy subjects during a 3-h recording¹⁰ but can be stimulated with octreotide.¹⁶

Tests for absorption

The D-xylene test and fecal fat estimation were done as described earlier.¹⁷,¹⁸

Criteria for diagnosis

Standard criteria were used for diagnosis of celiac disease,¹⁹ giardiasis, strongyloidiasis, Crohn's disease, amyloidosis, intestinal lymphangiectasia, IPSID, and hypogammaglobulinemia. Intestinal tuberculosis required demonstration of acid-fast bacilli (AFB) in intestinal tissue or extra-intestinal sites, and response to antimicrobial therapy; SIBO; jejunal aspirate colony count \( \geq 10^6 \) colony forming units (CFU)/ml. positive glucose hydrogen breath test or both; acquired immunodeficiency syndrome: anti-HIV antibodies by two enzyme immunoassays and CD4 T cell count < 200/μL; TS: absence of a specific cause for MAS, and persistent response to treatment with antibiotics and folic acid. In patients with TS, care was taken to exclude another cause for MAS by the above tests. Patients in whom work-up was incomplete were classified in idiopathic group.

Treatment and follow up

Patients were followed up regularly in the clinic. Specific treatment was given as indicated. Patients with TS and SIBO who did not respond to tetracycline were treated with another oral antibiotic based on the sensitivity of bacteria isolated from their jejunal aspirate. All patients also received nutritional advice and supportive treatment, as required.

The parameters evaluated for response during follow-up visits were frequency of diarrhea, body weight, hemoglobin and serum albumin levels, urinary excretion of D-xylene; and duodenal/jejunal histology (in 10 patients who agreed). The institution Ethics Committee approved the study protocol.

Statistical methods

Intergroup comparisons of continuous data were done using t test for unpaired data or one-way analysis of variance (ANOVA), as applicable. Variables found significant on ANOVA were subjected to post-hoc comparison between each pair of groups by Scheffe test. Differences in various categorical variables were analyzed using \( \chi^2 \) test with Yates' correction as applicable. p values below 0.05 were considered significant.

Results

The demographic, clinical and biochemical profile of 99 patients with MAS (age 34.6 [9.1] y; 59 men) is shown in Table 1. Diarrhea was the predominant symptom; three patients who presented without diarrhea included two with Crohn's disease and one with ileo-transverse anastomosis with SIBO. Nutritional deficiency in the form of pedal edema was present in one-quarter, and two-thirds had anemia (Table 1). Body mass index was low in most patients. Patients passed a mean of 508 g stool/day (range 260 to 1166). Community physicians had treated 28 patients with anti-tubercular drugs empirically in the past.

The etiological profile of MAS is shown in Table 2. TS (39/99; 39%) was the commonest cause of malab...
Table 2: Etiological profile and follow up of patients with malabsorption (n=99)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Initial response</th>
<th>Stools/d</th>
<th>Parameters at end of follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hb (g/dL)</td>
</tr>
<tr>
<td>Tropical sprue (39)</td>
<td>8</td>
<td>2 (1)</td>
<td>6.2 (2.2)</td>
</tr>
<tr>
<td>Crohn's disease (9)</td>
<td>7 (1 died)</td>
<td>2 (1-3)</td>
<td>5.5 (2-9)</td>
</tr>
<tr>
<td>Celiac disease (9)</td>
<td>8</td>
<td>2 (1-3)</td>
<td>6.5 (16)</td>
</tr>
<tr>
<td>Gastroitis (8)</td>
<td>8</td>
<td>2 (1-3)</td>
<td>6.5 (4-10)</td>
</tr>
<tr>
<td>Primary SIBO (8)</td>
<td>6</td>
<td>2 (1-3)</td>
<td>5.5 (4-18)</td>
</tr>
<tr>
<td>Intestinal tuberculosis (4)</td>
<td>1</td>
<td>2 (1-3)</td>
<td>7.5 (6-16)</td>
</tr>
<tr>
<td>AIDS (2)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Amyloidosis (2)</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IL (1)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Panhypogammaglobulinemia (2)</td>
<td>1</td>
<td>1</td>
<td>3 (1-4)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or median (range). *D-xylene excretion at follow up in patients with TS was 0.88 (0.25) (g/dL). IL: Intestinal lymphangiectasia; SIBO: Small intestinal bacterial overgrowth.

Discussion

Our study shows that TS is still the major cause of sporadic MAS in adults in this part of the country, with celiac disease and Crohn's disease being other important causes, whereas IPSID is rare.

The diagnosis of MAS was convincing in most of our patients. Though a small proportion of patients had normal fecal fat excretion, they had other laboratory evidence of malabsorption in addition to clinical features. The mean level of fecal fat excretion, though lower than the upper limit of normal, was only marginally high; similar values have been reported in some previous studies that explained it on the basis of restriction of dietary fat by the patient themselves.

In studies from southern India in the 1970s, TS was reported to be the commonest cause of chronic diarrhea. It is now believed that the frequency of TS is...
decreasing, possibly due to an improvement in sanitation and increasing use of antibiotics. However, this belief is not based on any firm data. In our study, TS was found to be a major cause of sporadic MAS in northern Indian adults. It is unlikely that we overestimated the frequency of TS. Instead, it is possible that some patients in the idiopathic group were actually suffering from TS, since a large proportion of them responded to antibiotics. We did not diagnose TS in these patients, because duodenal biopsy showed normal villous morphology.

It is possible that some of the patients included in the idiopathic group could be suffering from diarrhea-predominant irritable bowel syndrome. This may explain normal 24-h excretion of fat in stool in 6 of them, and absence of villous atrophy in duodenal biopsy; D-xylose test colorimetric method is known to be fallaciously low in some patients in the absence of MAS. Patients with irritable bowel syndrome are also known to have SIBO, which may explain response to antibiotics. Patients with other causes of MAS like celiac disease are also known to respond to antibiotics, at least temporarily, as a proportion of patients with MAS due to another cause may have SIBO secondary to intestinal stasis. In fact, secondary SIBO in patients with celiac disease may cause nonresponsiveness to gluten-free diet; these patients responded to addition of antibiotics. This suggests that response to antibiotics, which has been used as an important criterion for the diagnosis of TS, may not be a specific feature.

Crohn's disease was a common cause of MAS in our patients. In the recent past, there are increasing reports of this disease from India. In a report from southern India, 20% of patients with Crohn's disease presented with diarrhea. All these patients had received empirical anti-tubercular treatment without any response. We believe that Crohn's disease might be more common and is often misdiagnosed as intestinal tuberculosis. Nine of 30 patients with Crohn's disease in our clinic had MAS (unpublished data).

Celiac disease is reported to be the commonest cause of MAS in Indian children aged 2-15 years. Our study suggests that it is a common cause of MAS in Indian adults too. Late age of onset of diarrhea, absence of anemia, absence of growth failure, and initial response to antibiotics may be misleading. As most patients with subtotal villous atrophy turned out to have celiac disease, presence of this finding should alert clinicians about this possibility in adults with MAS.

Intestinal tuberculosis was found in 4% of patients with MAS. This suggests that tuberculosis may not be a common cause of MAS in India. However, a possibility of selection bias cannot be excluded; empirical trial with anti-tubercular treatment is common among community physicians, leading to under-representation of patients with this disease in such centers. In fact, 28% of our patients with MAS had previously received anti-tubercular treatment. Others have made similar observations about anti-tubercular treatment for patients with MAS due to causes other than intestinal tuberculosis. None of our patients with tuberculosis had intestinal obstruction as clinical presentation and all of them responded to anti-tubercular treatment. This is contrary to previous studies that have suggested that clinical MAS is rare in patients with intestinal tuberculosis in the absence of obstructive lesion.

No patient in the present series had IPSID, even though histology of intestinal biopsy was carefully evaluated and abnormal alpha heavy chain was looked for in 39 patients. This suggests that IPSID is relatively infrequent as a cause of MAS in India. To the best of our knowledge, only 27 well-documented patients with IPSID have been reported from India till date.

In conclusion, TS was the commonest cause of sporadic MAS in adults in a tertiary referral center in northern India. Celiac disease and Crohn's disease were the other common causes.

References

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**The 2nd S R Naik Memorial Workshop on ‘Research Methodology’ will be held in Lucknow August 28 and 29, 2004**

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