ORIGINAL ARTICLES

Spectrum of Malabsorption Syndrome In North Indian Children

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Abstract

Aims: To know the spectrum of malabsorption syndrome (MAS) in infants and children and highlight age-wise differences in etiology in different age groups.

Methods: 137 children presenting with diarrhea of more than 3 weeks' duration and/or growth failure and abnormality of one of more tests of malabsorption were studied. Etiology of MAS was determined using investigations specific for each of the causes.

Results: Sixty two (45%) children were below 2 years of age and 75 (55%) above. Common causes of MAS were: protracted diarrhea 45 (33%), celiac disease 35 (26%), parasitic infestations 13 (9%), milk protein intolerance 8 (6%), intestinal tuberculosis 7 (5%). In 18 (13%) patients, cause of MAS could not be determined. Protracted diarrhea (73%) and milk protein intolerance (13%) constituted the major etiology of MAS in children below 2 years of age, whereas celiac disease (43%), parasitic infestations (15%) and intestinal tuberculosis (9%) were the common causes in children above 2 years of age.

Conclusion: The spectrum of MAS in Indian children in different age groups is distinctly different from that seen in developed countries. (Indian J Gastroenterol 1993; 12: 120-5).

Key words: Protracted diarrhea, celiac disease, intestinal tuberculosis, giardiasis, milk protein intolerance.

Introduction

Causes of malabsorption syndrome (MAS) vary in different age groups and in different geographical areas. In developed countries, celiac disease, milk protein intolerance, celiac disease, congenital absorptive defects and primary immune defects are common causes of MAS in childhood. However, some diseases like cystic fibrosis are uncommon in non-Caucasian populations, and the prevalence of parasitic infestations depends on socioeconomic factors. To the best of our knowledge there is no published report from our country on the spectrum of MAS in infants and children. We describe here our hospital-based experience of MAS in North Indian children. Further, we have tried to highlight the differences in the etiology of MAS between children below and above 2 years of age since this may help in deciding an appropriate diagnostic and therapeutic approach to these children.

Methods

Inclusion criteria

Medical records of children under 15 years of age admitted to the Pediatric Gastroenterology Section of the Nehru Hospital, Chandigarh between August 1984 and December 1989 with clinical features suggestive of MAS were evaluated retrospectively.

Children fulfilling the following two criteria were included in the study: (i) diarrhea for more than 3 weeks and/or growth failure, and (2) biochemical evidence of malabsorption, ie one or more of the following: (i) increased fecal fat excretion, (ii) low serum and/or urine D-xylene, (iii) abnormal Schilling test, or (iv) evidence of disaccharide malabsorption (defined later).

Methods for tests of malabsorption

Fecal fat excretion was estimated after supplementing the diet with 2 g/Kg/d (minimum 30 g/d in infants below 2 years of age and 50 g/d in children above 2 years) of butter. Fecal fat excretion of more than 4.5 g/d in stool was considered as abnormal.

Urinary excretion of D-xylene was measured after an oral dose of 5 g. In patients with borderline 5 h urinary excretion values, 1 h serum D-xylene levels were estimated by repeating the test. Urinary excretion below 1.25 g/5 g of D-xylene or 1 h serum level of less than 20 mg/dL was considered abnormal.

A 24-h urinary excretion of less than 7% of an orally administered tracer dose of cyanocobalamin was considered as abnormal Schilling test.

Disaccharide malabsorption was defined as the presence of reducing substances (0.5% or more) in the stool and stool pH < 6.0 in children below 2 years of age.
In children above 2 years of age, lactose tolerance test was used and a blood glucose rise of ≤20 mg/dL after a lactose load of 50 g/m² was considered abnormal.

**Determining etiology of MAS**

Depending upon the clinical setting, patients were individualized for appropriate investigations to determine the etiology of malabsorption. Patients with primary malnutrition (malnutrition resulting from inadequate dietary intake prior to onset of symptoms) were excluded. Small intestinal biopsy was performed either using a pediatric Crosby capsule or through a fiberoptic gastroduodenoscope (Olympus GIF P2 or P3) from the second part of the duodenum. Stool examination for ova and cysts was done on three occasions in every case. Other investigations like rectal biopsy, barium meal studies, duodenal aspirate examination for *Giardia lamblia* trophozoites, sweat chloride test, blood transfusions cultures, etc were done in selected cases, wherever appropriate.

**Definitions**

The criteria used for diagnosing various causes of malabsorption were as follows:

- **Celiac disease.** (1) Presence of (a) diarrhea and/or growth retardation, (b) abnormal malabsorption test(s), and (c) villous atrophy on small bowel biopsy at initial presentation with (2) cessation of diarrhea, correction of anemia, improvement in growth parameters and improvement in tests of absorption with or without histological improvement on repeat small intestinal biopsy on institution of gluten-free diet.

- **Milk protein intolerance.** (1) Definitive temporal relationship between introduction of bovine/soy milk feeds and onset of diarrhea, (2) symptomatic improvement on withdrawal of milk from the diet, and (3) relapse of symptoms on reintroduction of milk.

- **Intestinal tuberculosis.** (1) Clinical evidence of intestinal tuberculosis, (2) evidence of tuberculosis elsewhere in the body, and (3) response to antitubercular therapy without relapse when drugs were withdrawn on completion of therapy. Diagnosis of tuberculosis elsewhere in the body was made using chest X-ray, Mantoux test, ESR, fine needle aspiration cytology and/or biopsy of accessible lymph nodes.

- **Cystic fibrosis.** Sweat chloride concentration of more than 60 mEq/L in an appropriate clinical setting.

**Results**

MAS was diagnosed in 137 patients who constituted 6.5% of 2085 admissions to our unit during the study period. Of these, 62 (45%) were below 2 years of age. The male to female ratio was 1:8. Various causes of MAS in different age groups are shown in Table 1. Characteristics of children with MAS are given in Table 2.

Forty-five children had disaccharide malabsorption. These constituted 33% (45/137) of all children with MAS.

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Below 2 years</th>
<th>2-15 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Protracted diarrhea *</td>
<td>45 (73)</td>
<td>0 (0)</td>
<td>45</td>
</tr>
<tr>
<td>Milk protein intolerance</td>
<td>8 (12)</td>
<td>0 (0)</td>
<td>8</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>8 (5)</td>
<td>32 (43)</td>
<td>35</td>
</tr>
<tr>
<td>Parasites*</td>
<td>2 (3)</td>
<td>11 (15)</td>
<td>13</td>
</tr>
<tr>
<td>Intestinal tuberculosis</td>
<td>0 (0)</td>
<td>7 (9)</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4 (6)**</td>
<td>7 (9)***</td>
<td>11</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>18 (24)</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>62 (100)</td>
<td>75 (100)</td>
<td>137</td>
</tr>
</tbody>
</table>

* *Giardia lamblia* 12, *Isospora* 1.

** Short bowel syndrome 2, *acrodermatitis enteropathica* 2.

*** Cystic fibrosis 2, tropical sprue 2, *trichinella* 1, nodular lymphoid hyperplasia 1, isolated late-onset lactase deficiency 1.

+ By definition occurs below 2 years of age. All cases had secondary disaccharide malabsorption.
Table 2: Characteristics of children with various causes of MAS

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Mean age at presentation (yr)</th>
<th>Number (%) with abnormal tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hb &lt; 10 g/dL</td>
</tr>
<tr>
<td>Milk protein intolerance</td>
<td>1.3</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>6.3</td>
<td>31 (89)</td>
</tr>
<tr>
<td>Parasitic infestation</td>
<td>5.3</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5.2</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>4.2</td>
<td>12 (67)</td>
</tr>
</tbody>
</table>

All these 45 children had secondary disaccharide malabsorption and were below 2 years of age, with mean age at presentation of 6.9 mo (range 1-24 mo). These children fulfilled the criteria for protracted diarrhea (diarrhea of >3 weeks duration in children below 2 years of age with weight loss during the illness).\textsuperscript{10} Candida albicans (pathogenic form) was grown from 12 cases (26.7%) while bacterial pathogens were detected in 18 cases (40%). Of these patients, bacteria were grown from stool alone in 14, from blood and urine besides stool in one case each, and from blood only in two. The bacterial isolates in decreasing order of frequency were Escherichia coli, Klebsiella pneumoniae, Shigella sp, Pseudomonas aeruginosa, Clostridium difficile and Staphylococcus aureus. These children required intensive management besides good nutritional support. Of these, 43 cases recovered; two children with septicaemia died.

Milk protein intolerance was diagnosed in 8 (6%) children. Of these, seven patients had intolerance to protein of buffalo milk and one to soya milk alone. All these children had gradual onset of symptoms of diarrhea which had become persistent. None of these cases had clinical or laboratory evidence of disaccharide malabsorption. All had microcytic hypochromic anemia. Three patients had family history of allergy, two had eosinophilia (absolute eosinophil count above 1000/μL) and three had occult blood in stool. Rectal biopsies were done in all the cases. Features of colitis with eosinophilic infiltration on rectal biopsy were noted in two children. Following milk withdrawal these patients showed clinical response over 7-22 days (mean 14.7). At 4 to 5 weeks all were diarrhea-free. On reintroduction of milk all had recurrence of diarrhea which abated on milk withdrawal.

Celiac disease was diagnosed in 35 (76%) cases. Of these, 3 children were below 2 years of age. Chronic diarrhea and growth failure were major presentations of celiac disease in 33 cases while 2 children presented with growth retardation and anemia. Small intestinal biopsy in all children showed moderate to severe villous atrophy (Fig 1). On gluten-free diet, these children had cessation of diarrhea and improvement in hematological and growth parameters. However, on follow-up, abnormalities in fecal fat excretion and D-xylene test persisted in 3 (6.6%) and 1 (2.1%) cases respectively. Histological improvement (Fig 2) was noted in 14 of 32 patients (44%) who underwent a repeat biopsy after 6-24 months of gluten-free diet.

Malabsorption attributable to various infestations was noted in 13 (9%) children. Giardia lamblia

Fig 1: Microphotograph showing crypt hyperplastic severe villous atrophy as diagnostic of celiac disease. (H & E, X100)
Fig 2: Microphotograph showing mucosal recovery as evident by near normal villi and crypts following 6 months of gluten-free diet. (H & E, X35)

trophozoites were detected in duodenal aspirate in 12 cases. Among these children two patients had mild villous atrophy and in two others, serum immunoglobulin (IgA and IgG) levels were low. Complete remission of symptoms was achieved with metronidazole therapy in patients of giardiasis. Duodenal biopsy showed Isospora belli infection in one child, who improved with cotrimoxazole therapy.

Intestinal tuberculosis was diagnosed as a cause of MAS in seven (3%) children, all of them above 2 years of age. Four cases each had Mantoux test positivity (15 mm induration at 72 h) and chest x-rays suggestive of tuberculosis. Barium meal follow-through examination showed malabsorption pattern in three children. Segmental small bowel dilatation (jejunum 2, ileum 1) was noted in 3 cases; one additional child had matted small bowel loops. One child had ascitic form of tubercular peritonitis. All the children with tuberculosis responded to antitubercular therapy given for 18 months. In addition, three patients with strictures required surgical stricturoplasty.

Other causes of MAS are shown in Table 1 under miscellaneous group. Two children had malabsorption due to short bowel syndrome which resulted from ileal resection for ileal atresia. Two patients with celiac disease enteropathy had clinical features of MAS in association with skin lesions and had complete response with zinc therapy. Both these infants had abnormal D-xylose test.

The etiology of MAS could not be established in 18 (13%) cases. All these children were malnourished despite adequate intake. Only 2 children in this group had villous atrophy on small intestinal biopsies. None of these patients improved on gluten and milk withdrawal from the diet. Their liver function tests and ultrasound examinations of liver, biliary tract and pancreas were normal.

Discussion

Secondary disaccharide malabsorption was the predominant cause of MAS (73%) among children below 2 years of age. All these children fulfilled the criteria for protracted diarrhea. Though disaccharide intolerance is described as the commonest cause of malabsorption in children, these cases are scarce in reported series of malabsorption from Western countries. The reason may be absence of prolonged illness due to quick, appropriate intervention in well nourished children.

Infection by bacteria was found in 40% and by fungi in 26.7%, with a mortality of 4.5%. The vicious cycle of mucosal injury, infection and acute malnutrition was probably responsible for perpetuating the diarrhea in young children with subclinical malnutrition. In a recent study from India nearly half of the children diarrhea below 2 years of age with protracted had disaccharide intolerance while in 25% pathogenic bacteria could be isolated. This group of patients with malabsorption constitute a high risk group and require urgent intervention.

Milk protein intolerance as a cause of malabsorption and chronic diarrhea due to mucosal injury in young children is well established. Rigid diagnostic criteria for this disease have been proposed to avoid overdiagnosis. However, remission of malabsorptive diarrhea on withdrawal of milk in the absence of disaccharide intolerance and reappearance of symptoms on reintroduction of milk appears to be a reasonable and practical guideline.

Presence of peripheral eosinophilia and of stool occult blood positivity (present in only 25% each of our patients) may also be helpful. Association of enteropathy and colitis though infrequent is well known. Recanal biopsy provided objective evidence for diagnosing colitis in 2 patients in our series. Intolerance to soya protein has been previously reported in 30-40% of patients with milk intolerance and was present in one of our eight patients. Hence, soya products may be unsuitable as milk substitutes in these patients.

Both the infants with celiac disease enteropathy had malabsorption. Although serum zinc levels could not be measured, the response to dietary zinc replacement was convincing. Whether or not there was a genetically determined zinc absorption defect with or without low intake could not be determined. However, other comparable patients did not develop such cutaneous features despite prolonged diarrhea.

Celiac disease enteropathy is a rare autosomal recessive disorder of zinc absorption leading to chronic diarrhea and characteristic skin lesions. The term also applies to any acquired zinc-deficiency state resulting in the same clinical picture. Oral zinc therapy results in

MILABSORPTION IN INDIAN CHILDREN – YAGHIA ET AL

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rapid and complete clinical remission.

Ninety-two percent of our patients with celiac disease had onset of symptoms after 2 years of age in contrast to the West where most cases are symptomatic before 2 years. This may be related to prolonged breast and top feeding and delayed introduction of gluten in Indian babies. A similar late age of presentation has been reported recently from England with a change in infant feeding practices. However, delayed in seeking medical care, as observed in Chile, cannot be ruled out. On gluten-free diet all children with celiac disease showed symptomatic, anthropometric and hematologic improvement. Malabsorption parameters became normal in 31 (89%) children. Of the 32 children who underwent repeat small intestinal mucosal biopsy while on a gluten-free diet, 31 (97%) did not show reversal of changes. This may be due to morphologic differences in the small intestinal mucosa of children from the tropics and those from the temperate zone. Abnormal small intestinal mucosal histology and subclinical malabsorption are known in residents of the tropics. Similar observations have been made previously from India. Non-adherence to gluten-free diet and existence of irreversible changes have been postulated to explain this persistence of villus changes.

The suitability of the ESPGAN (European Society of Pediatric Gastroenterology and Nutrition) criteria for diagnosis of celiac disease for use in the tropics may be questioned in view of the accumulated evidences. Gluten rechallenge studies, which have recently been questioned, were not performed in our cases. Eighty-two percent of patients had abnormal Schilling tests. Extensive involvement of the small intestine as evidenced by abnormal fecal fat excretion in 66% of our patients may explain this high incidence of Schilling test abnormality. Bacterial overgrowth and secondary malnutrition may be other factors responsible for abnormal Schilling test in our patients.

Malabsorption due to Giardia lamblia infestation is well known. However, considering the large number of children in the tropics harboring giardia, malabsorption due to this cause is relatively uncommon. Persistent giardiasis is known to be associated with agammaglobulinemia. All the children became symptom-free with treatment. Awareness of this condition as a cause of malabsorption may avoid many expensive tests.

Stasis due to tubercular enteritis or strictures, loss of mucosal surface and lymphatic block, alone or in combination, have been implicated as the mechanisms of malabsorption in patients with intestinal tuberculosis. Obstructive lesions are more commonly associated with malabsorption. Though overt stricture(s) were present in only three of our seven patients, a non-critical narrowing with stasis might have been responsible for the malabsorption in others.

Malabsorption due to cystic fibrosis is usually diagnosed before 2 years of age.10 Our full blown cases of cystic fibrosis were diagnosed late due to delay in seeking medical care. Tropical sprue has been previously described in children.11 Similar clinical picture may also occur in children with primary malnutrition. However, in our cases, dietary intake was adequate and there was a progressive deterioration in malabsorption with villous atrophy on jejunal biopsy which responded to antimicrobial drugs and folic acid therapy, fulfilling the diagnostic criteria for tropical sprue. In our experience, tropical sprue is a rare cause of malabsorption in childhood.

We could not pinpoint the underlying cause of malabsorption in 18 patients. The site of disease was intestinal mucosa as evidenced by deranged malabsorption tests and absence of hepatic and pancreatic diseases. Only 2 patients had mild to moderate villous atrophy. Whether these patients represented a complex interaction of subclinical malnutrition and infection or were forerunners of tropical sprue at a later age is open to question.

We conclude that protracted diarrhea, celiac disease, parasitic infestations and intestinal tuberculosis are common causes of MAS in Indian children. Besides, there is a distinct age-wise difference in etiology of MAS, protracted diarrhea resulting in secondary disaccharide intolerance being the major cause below 2 years of age and celiac disease, giardiasis and intestinal tuberculosis above 2 years. The spectrum of diseases responsible for MAS in Indian children is different from that described from the developed countries.

References
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