Coeliac Disease in Indian Children: Assessment of Clinical, Nutritional and Pathologic Characteristics

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ABSTRACT

Coeliac disease is an important cause of chronic diarrhoea, failure to thrive, and anaemia in children. Little information on the disease is available in India. This study was undertaken to determine the prevalence, clinical, anthropometric and histological profiles of coeliac disease in patients attending a tertiary referral centre in India. Coeliac disease was diagnosed in 42 (16.6%) of 246 children with chronic diarrhoea, failure to thrive, and anaemia. The mean ages at onset of symptoms and at diagnosis were 2.4 (range 0.5-10) years and 8.3 (range 3-14) years respectively, and a mean period of delay in diagnosis was 5.9 (range 1-13.5) years. Of the 42 cases, history of failure to thrive was observed in 38 (90%), chronic diarrhoea in 37 (88%), and anaemia in 6 cases. Short stature, under-nutrition, anaemia, oedema of feet, rickets, clubbing of fingers, features of vitamin A deficiency, and B-vitamin deficiency were found in 42, 26, 38, 9, 8, 6, 3, and 2 cases respectively. Onset of symptoms, such as, chronic diarrhoea and failure to thrive, was earlier in children with subtotal villous atrophy than in those with partial villous atrophy (mean±SD; 2.00±1.46 years vs 3.30±2.72 years; p<0.05). Results of the study suggest that coeliac disease is not uncommon in Indian children. Coeliac disease should be considered in the differential diagnosis, particularly in children without any symptoms of diarrhoea.

Key words: Coeliac disease; Diarrhoea; Diarrhoea, Infantile; Anaemia; Infant growth; Child growth; India

INTRODUCTION

Coeliac disease is an enteropathy characterized by damage to small intestinal mucosa due to ingestion of dietary gluten in genetically-susceptible individuals. Its prevalence varies in different geographical areas (1). The disease is considered rare in India and was first reported about a century ago (2). Variations in feeding and weaning practices and prevalence of malnutrition-related enteropathy warrant suspicion about coeliac disease and proper evaluation of children presenting with these symptoms.

Some studies conducted in India on coeliac disease have several limitations (2-6). These include: small number of patients, isolated study groups of protracted or chronic diarrhoea, or malabsorption syndrome, and lack of systematic diagnosis of the disease. We, therefore, studied childhood coeliac disease in a hospital-based population specifically evaluating clinical profile, nutrition status, and pathologic changes.

MATERIALS AND METHODS

Children with chronic diarrhoea (defined as an increase in frequency and liquidity of stools above the norm for
that child for three or more weeks), failure to thrive, and unexplained anaemia, who were referred to paediatric gastroenterology services of Sanjay Gandhi Postgraduate Institute of Medical Sciences between July 1991 and June 1999, were examined for coeliac disease. This hospital is a tertiary care centre providing advanced diagnostic and treatment facilities for referral cases.

On admission, history of illness was taken, and clinical evaluation and anthropometric assessment were done. Dietary evaluation included feeding history, age at introduction of gluten-containing diets, quantitative assessment of calories and protein intake, relationship of specific diets to symptoms, and relief of symptoms, if any, following withdrawal of specific dietary item. Weight and height indices were expressed as standard deviation (z-scores). Children having height standard deviation score less than zero were considered to have short stature. Nutrition status was also assessed by weight-for-height percentage. Patients with weight-for-height scores of less than 90% were considered undernourished. All anthropometric data were assessed in relation to standard for Indian children (7,8). Thorough evaluation was done to rule out concurrent systemic illnesses.

Faecal fat was estimated either by Van de Kamer's quantitative method (9) or by Sudan III staining (faecal fat microscopy) (10). For the quantitative method, diet was supplemented with butter (2 g/kg.d, >30 g/d in children aged less than two years and 50 g/d in children aged above two years. Faecal fat content >4.5 g/d or droplets >12/high-power field of microscope (Sudan III staining) were taken as abnormal (4,10). Blood and urinary D-xylose levels at one hour and over five hours after ingestion of 5 g of D-xylose respectively were estimated (normal >20 mg/dL and >1.25 g respectively) (4).

Endoscopic duodenal biopsy specimens (4-6 tissue pieces) were examined in all cases for the first time on admission to hospital. Biopsies were examined by light microscopy to evaluate the severity of villous atrophy (partial or subtotal), hyperplastic crypts, mononuclear infiltration of lamina propria, increased lymphohistiocytes, and infection with *Giardia lamblia*. The biopsy specimens were examined by a pathologist without having any knowledge of the clinical profile of the patients. Serum anti-endomysial IgA antibody test (11), using monkey esophagus as a substrate (the binding site, IFA kit, IgA), was added to our diagnostic evaluation at first presentation in new patients registered in our hospital after March 1998. Other tests, including haemogram, blood chemistry, coagulation parameters, stool microscopy, barium-meal follow through (if indicated), and x-ray wrist, were done.

Diagnosis of coeliac disease was based on the revised criteria of the European Society for Pediatric Gastroenterology and Nutrition, which include clinical features, characteristic histopathology with or without serology, and therapeutic response to gluten-free diet in eight weeks (12).

Based on the clinical features and small bowel histology, children with coeliac disease were categorized into two groups: (i) subtotal villous atrophy and (ii) partial villous atrophy. Children with coeliac disease were advised gluten-free diet which was formulated according to local food preference and cultural practice in India. The patients were given two lists of dietary items—one with food items whose consumption was permitted and the other that was prohibited. Patients and their parents were explained in detail the importance of dietary compliance. Patients were re-assessed eight weeks after initiation of gluten-free diet. Patients who responded to gluten-free diet were diagnosed as coeliac cases and were included in the study. Patients who did not respond to gluten-free diet were considered to have problems other than coeliac disease.

Statistical comparison of parameters in different groups was done by one-way ANOVA test.

**RESULTS**

Of the 246 children evaluated during the eight-year study period, 42 (21 boys) had coeliac disease (16.6%) giving a prevalence of five new cases per year. The mean ages at onset of symptoms and at diagnosis in hospital were 2.4 (range 0.5-10) years and 8.3 (range 3-14) years respectively. The mean period of delay in diagnosis was 5.9 (range 1-13.5) years.

Symptoms among patients (n=42) at the time of diagnosis were failure to thrive in 38 (90%), diarrhoea in 37 (88%), and anaemia in 6 (16%) cases. Abdominal pain, vomiting, pedal oedema, and delayed secondary sexual character development were observed in one case each. Children without diarrhoea (n=5) had failure to thrive in 2, anaemia with failure to thrive in 2, and abdominal pain and vomiting in one case(s).

At diagnosis, examination of patients revealed short stature in all children (mean height standard deviation score±SD of -3.35±1.52; range -6.45 to -0.24), under-
nutrition in 26 (62%), anaemia in 38 (90%), oedema of feet in 9, rickets in 8, and clubbing of fingers in 6 cases; and clinically-determined vitamin A and vitamin B-complex deficiencies in 3 and 2 cases respectively. One child also had splenic vein thrombosis. Mean haemoglobin at diagnosis was 64±36 (range 32-110) g/L. Urinary D-xylose done in 39 cases was abnormal in 36 (92%; mean value 0.70 g/5 g/5 h; range 0.19-1.20), and blood D-xylose done in other 3 patients was abnormal in 2 (mean value 16.03 mg/dL).

Thirty-three (94%) of the 35 children, who were subjected to faecal fat estimation, had abnormal fat excretion (mean value 5.64 g/d; range 4.7-17.1), while 7 patients subjected to Sudan staining had abnormal values (mean value 21.6 droplets/high-power field of microscope; range 13-32). Duodenal biopsies showed subtotal villous atrophy in 29 (69%) and partial villous atrophy in 13 (31%) of the 42 cases (Fig. 1). All biopsies showed hyperplastic crypts, increased lymphothe-liocytes, and mononuclear infiltration in lamina propria (Fig. 2).

Parameters of the height standard deviation score, duration of the disease, and weight-for-height between histological groups of subtotal villous atrophy (n=29) vs partial villous atrophy (n=13) were compared. No statistical differences were found in parameters of the height standard deviation score (mean±SD; -2.96±2.00 vs -2.59±1.6), duration of disease (mean±SD; 6.29±3.41 years vs 5.23±2.63 years), and weight-for-height percentage (mean±SD; 87.37±16.85 vs 89.76±12.20). There was a significant correlation between the age of onset of illness and the severity of histological damage (mean±SD; 2.00±1.46 years in the subtotal villous atrophy group vs 3.30±2.72 years in the partial villous atrophy group; p<0.05). One case also had G. lamblia-associated infection, which was treated. Anti-endomysial antibody (IgA) evaluation was done in 12 cases at diagnosis. Of these, 11 were positive (subtotal villous atrophy in 8 and partial villous atrophy in 3 cases).

All children had full compliance of gluten-free diet at initiation of therapy and then at follow-up periods of eight weeks and six months. Repeat duodenal biopsies were done to document histological improvement in 31 cases at completion of one year of gluten-free diet, or in later years. Of the 31 children, 22 had subtotal villous atrophy and 9 had partial villous atrophy at the time of diagnosis. Improvement from subtotal villous atrophy to partial villous atrophy was observed in 21 of the 22 (95%) cases, and in one case the finding returned to normal; marked histological improvement (decrease in crypt villous ratio, cellular infiltration, and decrease in intra-epithelial lymphocytes) was observed in other nine patients having partial villous atrophy.

Of the 31 cases subjected to second small bowel biopsy, two children had temporary dietary non-compliance one year before this biopsy. Eleven cases could not be subjected to repeat small bowel biopsy either due to lack of follow-up (n=5) or had not yet given consent (n=6) for second small bowel biopsy till the last follow-up.

**DISCUSSION**

The present study is a large series of well-documented cases of coeliac disease in Indian children describing the prevalence and clinical profile of the disease in this population. The prevalence of the disease in our study was 16.6% (42/246 evaluated cases). In previous studies done in India, its prevalence varied from 5% (3) to 6.8% (6). These studies had only evaluated children with protracted or chronic diarrhoea. In a special supplement
(13) based on compilation of guest lectures, 60 children with coeliac disease from one Indian centre have been quoted (unpublished data). Population-based studies in low-income countries reported the high prevalence of coeliac disease (14). Considering the frequency of 16.6% of coeliac disease among the children in our study, the myth about its infrequency among other categories of Indian population needs to be addressed.

There is a considerable variation in the age at onset of symptoms in coeliac disease manifesting at any time from infancy to old age (15-18). In our study, 45% of the children were symptomatic before the first two years of life, and other 55% were symptomatic after two years of age, which may be attributed to the prolonged breast-feeding practices and delayed supplementation of gluten in the diet of Indian children. Delayed onset of the disease in other developing countries with similar feeding practices supports our contention (19).

In the present series, the mean age at diagnosis was 8.3 years, suggesting delayed recognition of the disease. Similar delay has been reported (18,19) from both developing and developed countries (mean age at diagnosis 8.4 years vs 2.4 years respectively). One possible reason for the delayed diagnosis could be lack of awareness and non-availability of diagnostic tools. Sex ratio of 1.0 as shown by us is consistent with earlier reports from India (5,20). However, a female predominance has been reported by most studies from outside India (15,18). The frequency of common symptoms, such as failure to thrive (90%), diarrhoea (88%), and anaemia (n=6), was similar to those reported earlier from both developing and developed countries (4,15,18).

In the present series, five children had no diarrhoea; they presented with growth retardation, anaemia, and delayed puberty. A higher proportion of cases (20-40%) did not have diarrhoea in western studies (15,18,21). This may suggest that, in our country, patients with coeliac disease without diarrhoea may not seek medical treatment, and they remain undiagnosed (4). One of our cases had portal vein thrombosis, a rare association, which has previously been reported (22). Correct diagnosis and adequate response to diet modifications, particularly following a long duration of undiagnosed disease, gave a lot of confidence to these children and their families. Dietary compliance was, therefore, not a problem in these cases.

Most of our coeliac disease patients had abnormality of malabsorption tests (faecal fat in 95% and D-xylose in 90% cases). This suggests that children having features compatible with coeliac disease should all be screened by these tests; if found abnormal, further evaluation for the disease by small bowel biopsy and anti-endomysial antibody should be done. Histological involvement of small bowel ranges from mild mononuclear infiltration, villous atrophy of variable degree, and hyperplastic crypt stage to finally atrophic mucosa (23).

In our series, duodenal biopsies showed villous atrophy (subtotal villous atrophy in 69%, partial villous atrophy in 31%), hyperplastic crypts, increased lymphotheliocytes, and mononuclear infiltration in all cases. These observations are consistent with previous studies (4,23). We found that the patients with partial villous atrophy became symptomatic at a later age than those with subtotal villous atrophy. This finding is difficult to explain. It is possible that milder disease with less-severe mucosal damage does not show overt symptoms. Progressive increase in histological damage results in manifestation of symptoms at a later age. Earlier studies have shown variations in intestinal morphology in coeliac disease (23). Possible factors might be difference in host susceptibility (24) or variation in the amount of gluten load (25), which were not the focus of the present study.

In our study, coeliac disease constituted 16.6% of our patients, and there was a substantial delay in its diagnosis. Increased awareness about the disease is, thus, required for its early diagnosis, particularly in children presenting without any symptoms of diarrhoea.

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