Aims: To determine the prevalence of celiac disease (CD) in siblings of patients with this disease in Punjab, where wheat is the staple diet. Methods: Families of 80 patients with CD diagnosed as per modified ESPGAN criteria were offered family screening. Their siblings aged 2-15 years were tested for serum IgA anti-tissue transglutaminase antibody (anti-tTG) antibody. Those with positive or borderline test and some of those with negative test underwent endoscopic duodenal biopsy. Siblings with characteristics histological findings and showing improvement on follow-up were labeled as having celiac disease. Results: Of the 63 siblings of 48 index cases studied, 15 tested positive for anti-tTG; of these 13 had celiac disease. Three tested borderline for anti-tTG; none of them had CD. Of the 45 anti-tTG-negative subjects, two agreed to undergo biopsy; one of these had features of CD. Overall, 14 of 63 (22%) siblings had CD, including 8 who had no symptoms suggestive of CD. Conclusions: CD is common among siblings of patients with CD in Punjab, and may be asymptomatic.

Several studies have reported that celiac disease (CD) is more common in family members of patients with this disease than in the healthy population.1-5 In the first-degree relatives of probands, the prevalence rate of CD reaches 10%-20%.1,5

The inheritance of CD appears to be polygenic with a very high heritability, or a dominant inheritance with a very low rate of expression in heterozygotes.3 The concordance rate of CD among HLA-identical siblings is ~30%, mapping a great part of the genetic susceptibility to CD to the HLA region on chromosome 6.6 Evidence from different populations suggests that primary association of CD is with DQA1/b heterodimer encoded by the DQA1*0501 and the DQB1*0201 genes. Predisposition to CD has been mapped to HLA DQ2, which appears to a ‘dominant’ gene, and to HLA DQ8.7 No susceptibility genes other than HLA DQ have yet been identified.

There are few studies on the prevalence of CD amongst first-degree relatives of patients with CD in India. We therefore attempted to find the prevalence of CD among 1-15 year old siblings of patients with CD in Punjab, where wheat is the staple diet.

Methods

Patients with CD attending the Pediatric and Gastroenterology departments of our tertiary-care hospital between January 2003 and December 2004 were invited to have their siblings screened for CD. The diagnosis of CD was based on clinical presentation, characteristic small intestinal histology, raised anti-tissue transglutaminase (anti-tTG), and response to gluten withdrawal (modified ESPGAN criteria 1989). Of the 80 patients invited, 48 agreed. Of their 74 siblings, 63 underwent screening. After obtaining informed consent from their parents, detailed history and physical examination was recorded using a proforma, and a blood specimen was collected. The study was approved by the institutional Ethics Committee.

Serological screening

Serum IgA anti-tTG antibody was tested using an assay that used recombinant human tTG as antigen (Celikey™; Sweden Diagnostics,GmbH, Freiburg, Germany). Patients with anti-tTG levels less than 5.0 units/mL were labeled as negative, those with values between 5.0 and 8.0 as borderline, and those with values above 8.0 as positive.

Endoscopy and biopsy

Upper GI endoscopic biopsies were performed in subjects who tested positive or borderline for anti-tTG, as also in subjects with negative serology if they consented to it. In each subject, at least 4 specimens were obtained from the second part of the duodenum. Histology was assessed according to the modified Marsh classification.8,9 Children with histological abnormalities and who improved symptomatically such as with weight gain and showed improvement in hemoglobin on a minimum follow-up of two months, were labeled as having CD.

Pearson’s chi-square test (χ²), Z-test and Fisher’s exact test were used for analysis of the data.

Results

Of 63 siblings studied (34 boys), 15 tested positive...
and 3 tested borderline for anti-tTG (Fig). Of the 15 children with positive anti-tTG, 13 had histological changes suggestive of CD – 2 had Marsh II, 1 had Marsh IIIa, 2 had Marsh IIIb and 8 Marsh IIIc. Biopsies from two patients were normal, and showed neither villous atrophy nor increase in intraepithelial lymphocytes. All 3 children with borderline anti-tTG had normal intestinal histology.

Only 2 of the 45 siblings who tested negative for anti-tTG consented for endoscopic biopsy. Of these, one had histological changes suggestive of CD (Marsh IIIc). He had abdominal pain, malnutrition and anemia, and IgA deficiency was found retrospectively on serum immunoglobulin estimation; he improved with gluten-free diet.

Thus, of the 63 siblings screened, 14 (22%; 7 boys) were found to have CD. The prevalence rate in siblings aged ≥10-15 years (9 of 26) was higher than that in ≥5-10 year (5 of 24) and 1-5 year (0 of 13) age groups (p<0.05).

Clinical presentation amongst the index cases was with typical gastrointestinal symptoms (diarrhea, flatulence, abdominal discomfort) in 40 (83.3%), with the rest having delayed growth (n=5) and severe anemia (n=3). Amongst the 14 siblings diagnosed to have CD, 4 had typical gastrointestinal symptoms such as recurrent episodes of diarrhea, flatulence, abdominal discomfort, and one each had short stature and anemia; the remaining 8 subjects were asymptomatic. A higher percentage of affected siblings (10/14) were asymptomatic or without typical GI symptoms as compared to the index cases (8/48).

The diagnosis of CD among siblings was associated with weight less than 80% of the 50th percentile and height <90% of the 50th percentile of the National Center for Health Statistics standards developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000) http://www.cdc.gov/nchs/data/nhanes/growthcharts (Table).

### Table: Relationship of various clinical features with presence of CD among 63 siblings of patients with CD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Present</th>
<th>Absent</th>
<th>p value</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malabsorptive stools*</td>
<td>4</td>
<td>0</td>
<td>&lt;0.01</td>
<td>—</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>1</td>
<td>&lt;0.01</td>
<td>19.2 (16.5-27.7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7</td>
<td>5</td>
<td>&lt;0.01</td>
<td>8.8 (6.0-11.5)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>4</td>
<td>0</td>
<td>&lt;0.01</td>
<td>—</td>
</tr>
<tr>
<td>Pallor</td>
<td>10</td>
<td>8</td>
<td>&lt;0.01</td>
<td>12.8 (8.9-16.3)</td>
</tr>
<tr>
<td>Weight &lt;80% of 50th percentile of NCHS</td>
<td>10</td>
<td>7</td>
<td>&lt;0.01</td>
<td>15.0 (11.3-24.4)</td>
</tr>
<tr>
<td>Height &lt;90% of 50th percentile of NCHS</td>
<td>6</td>
<td>2</td>
<td>&lt;0.01</td>
<td>17.6 (13.7-26.5)</td>
</tr>
</tbody>
</table>

NCHS = National Center for Health Statistics

*Frequent, bulky, foul smelling and sticky stools that are difficult to flush off due to high fat content

### Discussion

Our data show that 22% of siblings of patients with CD in Punjab had this disease. This proportion is higher than that in family studies reported previously in the world literature.1-7 Further, our estimate of prevalence of CD among siblings may be an underestimate since small bowel biopsy, which is the gold standard for the diagnosis of CD, was done in only the seropositive and only 2 of the seronegative subjects.10 However, in a previous study, obtaining biopsies in all siblings did not result in detection of further cases with CD.11 The higher rate observed in our study may be related to selection bias, since parents of only 60% of the CD patients agreed to participate.

The prevalence of CD in siblings in the age group 10-15 years was highest, followed by the 5-10 years group; no positive case was detected in the 1-5 years age group. Even in index cases there was only one case with age less than 2 years. This is in accordance with previous studies in India in the general population, indicating a delay in the onset of symptoms and age of presentation.12,13 This delay is probably because of delayed weaning, late introduction of gluten, delayed referral, and lack of awareness about the disease. Interestingly, epidemiological studies in
Sweden and Croatia have suggested that there is a trend towards higher age of presentation of CD in the last decade. Our data depicting significant proportion of atypical or silent forms in siblings of index cases relates well to a recent study by Bomanico et al in Italy.

Two of our patients had anti-tTG levels just more than lower limit of positive range but had normal histological findings. Though these were labeled as not having CD, the possibility of ‘potential CD’ cannot be ruled out. Indeed, in a study of 25 such cases, Collin et al have shown that 30% developed villous atrophy over a period of 7 years.

Despite the limitation of small number of subjects studied, the present study provides evidence of high prevalence of CD in siblings of patients with CD in Punjab. Our data suggest the need for screening in the siblings of patients with CD since they may be at risk of complications of CD like growth retardation, osteopenia, infertility, autoimmune disease and malignancies.

References


