Gluten intolerance: Sex- and age-related features

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OBJECTIVE: Gluten intolerance is an immune-mediated enteropathy associated with gluten-containing foods in genetically susceptible patients. The typical form mainly affecting children shows failure to thrive and/or gastrointestinal symptoms. The adult form is less typical, presenting vague gastrointestinal symptoms, iron deficiency (with or without anemia) or non-specific serum chemistry abnormalities. The present study aims to analyze clinical and biochemical differences of celiac disease (CD) according to sex and age.

PATIENTS AND METHODS: The present study reviewed clinical and biochemical features of patients with suspected CD admitted to the Hospital General of Móstoles (Madrid, Spain) between July 2001 and June 2005. Two hundred fifty-two patients were analyzed, in whom intestinal biopsy was performed due to clinical and/or biochemical abnormalities suggestive of CD. One hundred seventy-eight asymptomatic relatives of the affected patients were also included. Overall, 125 patients showed diagnostic features of CD in the intestinal biopsy.

RESULTS: The results confirmed higher prevalence of typical forms of CD in children (67% in children compared with only 14.3% in adults). CD seemed to be more frequent in adult women than in men (ratio of women to men 4:1), but it is worth noting that men diagnosed were most often referred with a typical clinical picture, so atypical forms of the disease in men may have been underdiagnosed.

CONCLUSIONS: CD shows atypical features in adults, and physicians must include this disorder in the differential diagnosis of adult patients. CD seemed to be more frequent in adult women than in men (ratio of women to men 4:1), but it is worth noting that men diagnosed were most often referred with a typical clinical picture, so atypical forms of the disease in men may have been underdiagnosed.

Key Words: Age; Atypical forms; Celiac disease; Sex; Transglutaminase antibody

Celiac disease (CD) is an immune-mediated enteropathy caused by gluten-containing foods in genetically susceptible patients. Epidemiological studies (1-4) from the European Union and the United States indicate that CD is a frequent disorder that can affect 0.5% to 1% of the population. However, in many countries, the incidence seems to be much lower, a fact that we can attribute both to regional differences in the incidence of the disease and also to the underdiagnosis of the disorder, which can show many different clinical pictures (5-8). In recent years, the advances in serological tests for diagnosis have allowed for improved detection of atypical and silent variants of the disease (1,9).

The aim of the present study is to describe the age- and sex-related differences in the clinical manifestations of CD.

PATIENTS AND METHODS

Study population
Between July 2001 and June 2005, 7298 patients were referred to the laboratory at the Hospital General of Móstoles (Madrid, Spain) for determination of immunological markers of CD. Most of these patients (61.7%) were referred by the gastroenterology department, while 16.8% by the department of pediatrics, 16.7% by the department of medicine, and 4.4% by other departments.

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Differences between quantitative variables were assessed with the frequency, median and percentile (P5-95) values were included. A descriptive analysis of all the variables was performed, and statistical analysis was performed using a Mann-Whitney U test, and qualitative variables were compared with $\chi^2$ with Yates' correction.

### RESULTS

The demographic characteristics of the patients are summarized in Table 1. The CD group included 87 females (69.6%) and 38 males (30.4%). Ninety patients (59 female and 31 male) were younger than 15 years of age and 35 were adults (28 women and seven men).

The asymptomatic relatives group included 53 fathers, 55 mothers, seven sons and daughters of the patients, and 61 brothers or sisters; two of them were twins of patients with CD. In this group, 14 cases of CD were diagnosed with intestinal biopsy (8%), 10 in female patients and four in male patients. Of these CD patients, nine were children and five were adults; their relationship with the patient was one father, two mothers, seven brothers or sisters, two sons and daughters, and two twins.

The rate of CD was twice as high in women than in men for the overall population (the female to male ratio was 2.3), for the pediatric group (1.97) and for the relatives (2.5). However, in adults this ratio was much higher, reaching 4:1.

The rate of diagnosis tended to decrease with age, and as expected, the age group in which new cases of CD were most often diagnosed were in children under three years of age. Sixty-five cases (52%) of typical CD were found, but it is worth noting that 60 patients (48%) showed atypical manifestations of CD. Table 2 summarizes the clinical picture for the different age and sex groups. The classical clinical picture is significantly more prevalent in children than in adults (92.3% versus 7.7%; $P<0.001$). If we take into consideration only patients with atypical forms of CD (n=60), the age distribution is similar, with 50% (30 of 60) were children and 50% (30 of 60) were adults.

In terms of sex, male patients tended to show more frequently classical forms of CD (24 of 38 [63.2%] patients) while women (41 of 87 [47%] patients) showed an almost equal distribution. Nevertheless, the typical forms were found almost exclusively in children (38 of 63) and only in three adult women. Correspondingly, atypical CD mainly affects female patients older than 14 years of age (25 of 28; 89%). In male patients, similar analysis cannot be performed due to the small number of adults participating in the study.

For both sexes, the incidence of typical CD tends to decrease with age and this clinical form represents 78% of cases in children younger than three years of age for both sexes; 43% in
Signs and/or symptoms of celiac disease (CD) at diagnosis

<table>
<thead>
<tr>
<th>Signs and/or symptoms</th>
<th>Diagnosis</th>
<th>CD patients with a sign/symptom, n (%)</th>
<th>Children, n (%)</th>
<th>Adults, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>CD</td>
<td>64 (46.3)</td>
<td>59 (65.5)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>problems/failure to thrive, n=138</td>
<td>Non-CD</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>CD</td>
<td>15 (39.5)</td>
<td>7 (7.7)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>or without anemia, n=38</td>
<td>Non-CD</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others, n=47</td>
<td>CD</td>
<td>26 (56.5)</td>
<td>12 (13.3)</td>
<td>14 (40)</td>
</tr>
<tr>
<td>in risk groups, n=206</td>
<td>Non-CD</td>
<td>21</td>
<td></td>
<td>186</td>
</tr>
</tbody>
</table>

**Others** include hypertransaminasemia, endocrine diseases, infertility and aplastic stomatitis. Risk groups are relatives of CD patients, and patients with diabetes mellitus type I or Down Syndrome.

Table 3 compares the presenting symptoms of CD. Significant differences in clinical presentation were found according to age (P<0.001). Failure to thrive or low weight, and GI symptoms were more prevalent in children (almost 65.5% of all cases), while in adults, the predominant findings were abnormalities in the hepatic function tests (40%), followed by iron deficiency (22.9%), with a similar frequency in other risk groups (22.8%).

The main conclusions of our work are atypical, and silent forms of CD are much less frequent (14.3%). Failure to thrive or associated with GI symptoms, was much more common in children compared with adults (36 U/L versus 23 U/L; P=0.07), while AST values were significantly higher in adults than children (36 U/L versus 26 U/L; P=0.009).

Thirty-nine per cent of CD patients had low ferritin levels compared with 22% of the controls (P<0.014). There were no differences in ferritin levels according to sex. Nevertheless, the median ferritin level was significantly lower in adults with CD than in children (less than 15 µg/L versus 20 µg/L; P<0.001), a fact that could be attributed to the increased frequency of low ferritin levels in adult women compared with younger girls (31.4%; P<0.01).

**DISCUSSION**

The aim of the present study was to prospectively define the clinical features of CD and possible differences related to either sex or age. In the present study, the prevalence of CD was twice as high in women than in men. These results were consistent with those reported by Bardella et al (5). However, Green et al (10) used CD screening survey results taken from the general population and blood donors, which indicated that CD distribution was similar in men and women. We feel that this apparent contradiction may indicate that most studies performed in symptomatic patients are biased by population selection. Our results suggest that the sex difference in CD incidence could be real for the number of patients studied on clinical and/or immunological suspicion of CD, and is almost equivalent for both sexes (46% of male patients versus 54% of females patients in the control group and 48.9% versus 51.1%, respectively, in the asymptomatic relatives group); confirmation of CD with biopsy doubled in women compared with men. Nevertheless, we cannot consider this fact surprising, because many diseases with an autoimmune pathogenesis show a higher prevalence in women.

The prevalence of CD in asymptomatic relatives of CD patients has been estimated by some reports (5,11) to be between 5% and 10%. Our prevalence was 8%, therefore corroborating previous results on the issue.

Some authors have reported that the diagnosis of CD is not made until age 5 (10,12). However, in the present study, the frequency of CD diagnosis decreased with age. This apparent contradiction can be attributed to the fact that the clinical presentation is rather infrequent in this age group according to the literature.

There are not many data regarding prevalence of CD among children with typical or atypical forms of the disease. In the present study, the rate of CD among patients presenting with GI symptoms and/or abnormalities in weight or height was 46.3%. This contrasts with the situation in adults, in whom GI symptoms are much less frequent (14.3%). Failure to thrive or weight loss, associated or not associated with GI symptoms, was the main presenting symptom in children (34.7% in the present study). No adults reported weight abnormalities because they gave less importance to this symptom.

The most frequent presenting signs in adult patients were hypertransaminasemia and iron deficiency. It has been described that 15% to 50% of adults with atypical CD show increased levels of transaminases, and also, 95% of cases of unexplained increases in transaminases could be due to silent CD (13-15). In the present study, 57% of CD patients showed a moderate ALT increase compared with 23% of the controls (P<0.001), and this
We must also consider the fact that even vague symptoms in adults improve dramatically with a gluten-free diet, and patients have described improvements in their overall quality of life with diet (10). Almost 23% of CD adults belonged to risk groups (either relatives or patients with diabetes mellitus or Down syndrome); these data are also consistent with those reported by other authors (22% in the study by Green et al [10]). Serological screening would be especially important in the groups at risk of CD (23-24).

CONCLUSION

The results of the present study confirm clinical and laboratory differences in CD between children and adults, and also between both sexes. We feel that CD is widely underdiagnosed in our environment, mainly in adults and primarily in men. Although this low rate of diagnosis in adults can be attributed to the little importance given to the general vague symptoms of these patients, clinicians should begin to include CD in the differential diagnosis of hypertransaminasemia and iron deficiency in both children and adults, and stop considering CD as a disease found exclusively in children.

REFERENCES
