High Prevalence of Celiac Disease Among Patients Affected by Crohn’s Disease

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Background: Recent literature has shown a correlation between Crohn’s disease (CD) and celiac disease, but a prospective study has not been performed. Our aim was to evaluate the prevalence of celiac disease in a consecutive series of patients affected by CD, in whom the disease was diagnosed for the first time.

Methods: From January to December 2004, we diagnosed 27 patients affected by CD (13 men and 14 women; mean age, 32.3 yrs; range, 16–69 yrs). In all patients, we performed antigliadin, antiendomysium, and antitransglutaminase antibody tests, and the sorbitol H2 breath test evaluation. In case of antibodies and/or sorbitol positivity, esophagogastroduodenoscopy was performed for a small bowel biopsy.

Results: Antigliadin, antiendomysium, and antitransglutaminase antibody tests were positive in 8/27 (29.63%), 4/27 (14.81%), and 5/27 (18.52%) patients, respectively, whereas the sorbitol H2 breath test was positive in 11/27 (40.74%) patients: all of them underwent esophagogastroduodenoscopy. Nine of 11 patients showed signs of duodenal endoscopic damage, and 5/9 (55.55%) showed histologic features of celiac disease (18.52% of overall CD population studied): 2 showed Marsh IIIc lesions (1 patient affected by ileal CD and 1 affected by ileo-colonic CD), 2 showed Marsh IIIb lesions (all of them affected by ileo-colonic CD), 1 showed a Marsh IIIa lesion (1 patient affected by colonic CD).

Conclusions: Prevalence of celiac disease seems to be high among patients affected by CD, and this finding should be kept in mind at the time of the first diagnosis of CD; a gluten-free diet should be promptly started.

Key Words: antibodies, celiac disease, Crohn’s disease, sorbitol H2 breath test

Crohn’s disease (CD) is a chronic inflammatory disease of the intestine potentially affecting all parts of intestine, with predilection in the terminal ileum and proximal colon.1 Histopathologically, it is characterized by a discontinuous segmental manifestation and implication of all intestinal layers, while clinically it is characterized by a typical malabsorption syndrome.1

Celiac disease is also a chronic inflammatory disease of the gut occurring in genetically susceptible individuals after ingestion of gluten. It is characterized by flattened mucosa, villous atrophy, and crypt hyperplasia in the small intestine and by the classic malabsorption syndrome (diarrhea, steatorrhea, weight loss) or by minor apparently unrelated symptoms such as iron-deficiency anemia, osteopenic bone disease, amenorrhea, and infertility.2 The lack of gluten in the diet generally leads to a return to normality of the morphologic changes.3

Our recent experience4 and some recent case reports5–7 showed that there is a relationship between CD and celiac disease, but a prospective study has not been performed yet. The aim of our study was to evaluate the prevalence of celiac disease in a consecutive series of patients affected by CD, in whom the disease was diagnosed for the first time.

MATERIALS AND METHODS

From January to December 2004, we diagnosed 27 patients affected by CD (13 men and 14 women; mean age, 32.3 yrs; range, 16–69 yrs), in whom this diagnosis was made for the first time. Twelve patients showed ileo-colonic, 7 showed colonic, and 8 showed ileal localization of CD. In all patients, CD was diagnosed for the first time and had a definite diagnosis based on accepted radiologic, endoscopic, and if available (in 25 patients), histologic criteria.8 All patients had a small bowel barium enema and colonoscopy to assess disease localization.

After assessing diagnosis of CD, all were evaluated for celiac disease. In all patients, we performed an H2 sorbitol breath test (H2-BT) and antigliadin (AGA) antitransglutaminase (anti-tTG), and antiendomysium (EMA) antibody tests.

We measured serum levels of immunoglobulin A (IgA; reference range, 90–450 mg/dL) to exclude a condition of
selective serum IgA deficiency. IgA and IgG AGAs were measured in all patients by enzyme-linked immunosorbent assay (kit Alfa-glia test; Eurospital, Trieste, Italy); the lower limit of positivity of IgA class was 0.2 EU/mL and that of IgG class was 10.0 EU/mL. IgA anti-tTG antibodies were determined by enzyme-linked immunosorbent assay using human recombinant tTG (kit Eu-tTG; Eurospital); the lower limit of positivity of these antibodies was 7 AU/mL.

IgA EMAs were screened by the indirect immunofluorescent method on monkey esophagus (kit Antiendomysium; Eurospital). The lower limit of positivity of IgA class was 0.2 AU/mL and that of IgG class was 10.0 EU/mL. IgA anti-tTG antibodies were measured in all patients by enzyme-linked immunosorbent assay (kit Alfa-glia test; Eurospital, Trieste, Italy); the lower limit of positivity of IgA class was 0.2 EU/mL and that of IgG class was 10.0 EU/mL. IgA anti-tTG antibodies were measured in all patients by enzyme-linked immunosorbent assay using human recombinant tTG (kit Eu-tTG; Eurospital); the lower limit of positivity of these antibodies was 7 AU/mL.

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An H2-BT was performed in all patients as a measure of malabsorption assessment. The patients were studied after an overnight fasting having been instructed to consume a meal of rice and meat; they were requested not to smoke on the morning of the test. End expiratory samples were collected before the patients drank the test solution (5 g of sorbitol in 150 mL of tap water) and every 30 minutes for 4 hours.

An increase in H2 concentration of at least 20 ppm over fasting baseline was considered positive for sorbitol malabsorption. The cut-off for calculating the validity of the test was shifted every 30 minutes, and a response operating characteristics curve was plotted on the basis of the obtained results.

In case of antibodies and/or sorbitol positivity, and after receiving informed consent from the patients, esophagogastroduodenoscopy (EGDscopy) was performed for small bowel biopsy. At least 6 small bowel biopsies were obtained from the second part of the duodenum and evaluated by hematoxylin and eosin staining. Biopptic samples are not routinely obtained from duodenal bulb, but are performed in case of micronodular bulbs (an endoscopic finding suspected for celiac disease). Obviously, biopptic samples to detect villous atrophy were obtained not only in patients with an endoscopic aspect suspected for CD but also in patients with a normal endoscopic aspect. Endoscopic duodenal damage of the duodenum was classified as a normal endoscopic aspect (normal appearance of the duodenum), slight/mild endoscopic damage (micronodular bulb, granular mucosa of the second duodenal portion, scalloping of duodenal folds, reduction of duodenal folds), and severe endoscopic damage (“mosaic” pattern of mucosa in the second duodenal portion and loss of duodenal folds) according to our previous classification.

Celiac disease was defined as permanent gluten-sensitive enteropathy, primarily expressed by the presence of characteristic small intestinal lesions. The biopsies were read by an expert histopathologist who was blinded to the suspected celiac disease.

Histopathology was expressed according to the Marsh classification modified by Oberhuber: Marsh type I, “infiltrative” lesions with more than 30 lymphocytes/100 epithelial cells; Marsh type II, “infiltrative/hyperplastic” lesions; Marsh type III, “partial (sub)total villous atrophy (VA)”. We subdivided the Marsh type III into partial VA (Marsh IIIa), subtotal VA (Marsh IIIb), and total VA (Marsh IIIc).

Other possible causes of villous atrophy or duodenal damage, such as Giardia lamblia infection, tropical sprue, collagenous sprue, food protein hypersensitivity (cow’s milks, eggs, fish, rice, chicken) were excluded, as well as other causes of inflammatory infiltration of duodenum, such as peptic duodenitis.

RESULTS

AGAs were positive in 8/27 (29.63%) patients, anti-tTG antibodies were positive in 5/27 (18.52%) patients, and EMAs were present in 4/27 (14.81%) patients. The sorbitol H2-BT showed signs of malabsorption in 11/27 (40.74%) patients; according to our methods, all 11 patients showing sorbitol malabsorption underwent EGDscopy.

Nine of 11 patients showed signs of endoscopic damage (2 slight, 6 moderate, and 1 severe). Five patients undergoing EGDscopy showed histologic features of celiac disease (18.52% of the overall population with CD studied): 2 showed Marsh IIIc lesions (1 patient affected by ileal CD and 1 affected by ileo-colonic CD), 2 showed Marsh IIIb lesions (all of them affected by ileo-colonic CD), and 1 showed Marsh IIIa lesions (patient affected by colonic CD). Two of nine patients (7.40% of the overall population of CD studied) showed a reduction of duodenal folds but did not showed histologic features of celiac disease or duodenal localization of CD.

The clinical, serological, endoscopic, and histologic findings of the patients affected by CD and celiac disease are described in Table 1. In light of these results, we noted that AGAs were positive in 4/27 (14.81%) of patients affected by CD alone.

DISCUSSION

Some literature (and also our personal experience) report a correlation between CD and celiac disease. However, in most cases, this association was incidental (e.g., diagnosis of celiac disease was made because of irreversible diarrhea in CD after anti-inflammatory therapy had started). This is the first prospective study evaluating the prevalence of celiac disease in a consecutive series of patients affected by CD, and it leads to several interesting point of discussion.

First, the results of serological testing obtained from this study confirm some literature data.
TABLE 1. Characteristics of Patients Affected by CD and Celiac Disease

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Localization of CD</th>
<th>Duodenal Endoscopic Feature</th>
<th>Marsh Lesion</th>
<th>AGA</th>
<th>EMA</th>
<th>Anti-tTG</th>
<th>Sorbitol H₂-BT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>33</td>
<td>Ileo-colonic</td>
<td>Granular aspect of second portion</td>
<td>IIIb</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>Colonic</td>
<td>Scalloping of duodenal folds</td>
<td>IIIa</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
<td>Ileal</td>
<td>Absence of duodenal folds</td>
<td>IIIc</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Male</td>
<td>53</td>
<td>Ileo-colonic</td>
<td>Absence of duodenal folds</td>
<td>IIIc</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Female</td>
<td>53</td>
<td>Ileo-colonic</td>
<td>Reduction of duodenal folds</td>
<td>IIIb</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

1. AGAs show poor specificity because approximately 14% of patients affected by CD alone showed AGA positivity. These results confirm the recent study by Datele et al., who described AGA positivity in about 16% of patients affected by CD.

2. Despite recent data described by Datele et al. and Bizzarro et al., this study failed to show anti-tTG positivity in patients affected by CD. In fact, both studies described anti-tTG positivity in approximately 2% of patients affected by CD. However, guinea pig liver anti-tTGs were used in these studies, whereas we used human recombinant anti-tTG. This more advanced diagnostic assay seems to be more sensitive and specific than guinea pig liver anti-tTG and may explain our results.

3. Several patients affected by CD and celiac disease were seronegative for AGA and EMA, (see Table 1). This is particularly true for patients showing slight/moderate histologic damage of the duodenum (Marsh II–IIIa lesions), and it confirms recent literature data.

The second interesting point is represented by the effectiveness of sorbitol H₂-BT in assessing small bowel malabsorption. Sorbitol, a hexahydroxy alcohol used as a sugar substitute in many dietetic foods and as a drug vehicle, has been recently used to diagnose celiac patients, because its absorption. Sorbitol, a hexahydroxy alcohol used as a sugar substitute in many dietetic foods and as a drug vehicle, has been recently used to diagnose celiac patients, because its absorption.

Chronic inflammatory intestinal diseases are characterized by a chronic inflammation, especially in the lamina propria. The human gastrointestinal tract possesses a complex ecosystem, in which there is a correct balance between antigenic stimuli and immune response. Chronic inflammatory intestinal diseases are characterized by an up-regulation of the immunologic response, which may be T-helper type 1 (Th1: stimulation of type 1 immunity, which is characterized by intense phagocytic activity, but also stimulates moderate levels of antibodies production) or type 2 (Th2: stimulation of type 2 immunity, which is characterized by suppression of phagocytic activity and high antibodies titers) immunologic response. Both CD and celiac disease are related to the Th1 pathway, and both CD and celiac disease are characterized by a decreased cellular apoptosis, which provokes a chronic inflammation, especially in the lamina propria. This alteration is confirmed by caspase 8 reduction and under expression of BAX, which favors apoptosis resistance of intraepithelial T cells, as described both in CD and celiac disease. These findings seem to be related to interleukin (IL)-15 action. This cytokine shares biologic activities but no significant sequence homology with IL-2; it induces T-cell recruitment to the site of inflammation, T-cell proliferation, and cytokine production and rescue from apoptosis. IL-15 overexpression has been shown both in CD and celiac disease. Moreover, other cytokines involved in cell-mediated
immunopathogenesis [such as tumor necrosis factor α (TNFα), interferon γ, or IL-8] are increased in both diseases.24,32 and all these data confirm the possible common immunopathogenesis of both diseases.

However, why don’t all CD patients develop celiac disease? The first hypothesis is that these diseases show different human leucocyte antigen (HLA) susceptibility. We know that there is a strict relation between celiac disease and HLA-DQ2 and HLA-DQ8,53 whereas the relation between CD and HLA genes seems to be lacking.34 Therefore, only patients with CD showing HLA-DQ2 or -DQ8 could also develop celiac disease. However, another (for us, more intriguing) hypothesis is related to increased gut permeability in these diseases. We know that CD is characterized by increased gut permeability, which may be related to TNFα action,35 and it may provoke bacterial translocation as a consequence of bacterial overgrowth.36 Also, celiac disease shows increased gut permeability caused by zonulin reduction, a protein modeling intestinal permeability between tight junctions.37 The hypothesis explaining this association may be the following: the increased permeability in CD may expose several bacteria mimicking the 57–68 and/or 62–75 gliadin sequence, and enabling them, thanks to an increase of the cytokine network (IL-15, IL-2, TNFα, interferon γ), to cause a T,1 immunologic reaction with development of celiac disease lesions. This hypothesis seems to have been confirmed by the recent demonstration of high seroreactivity against Saccharomyces cerevisiae (the yeast bread), not only in CD, but also in celiac disease.38 It is possible that specific alimentary and/or bacterial antigens may cause celiac disease in patients affected by CD because of the T,1 pathway.

We conclude that CD shows a strict correlation with celiac disease, and this association should be kept in mind when a new case of CD is diagnosed. More accurate immunopathological studies should be performed to explain whether there is a common immunopathogenesis in these diseases.

REFERENCES


