

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

Antonio Tursi, MD,* Gian Marco Giorgetti, MD,† Giovanni Brandimarte, MD,‡ and Walter Elisei, MD,‡

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, anti-endomysium, 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

(*Inflamm Bowel Dis* 2005;11:662–666)

Received for publication January 15, 2005; accepted March 20, 2005.

From the *Digestive Endoscopy Unit, "Lorenzo Bonomo" Hospital, Andria, Italy; †Department of Internal Medicine, Clinical Nutrition Unit, "S. Eugenio" Hospital, Rome, Italy; and ‡Department of Internal Medicine, Division of Gastroenterology, "Cristo Re" Hospital, Rome, Italy.

Reprints: Antonio Tursi, Galleria Pisani, 4 70031 Andria, Italy (e-mail: antotursi@tiscali.it)

Copyright © 2005 by Lippincott Williams & Wilkins

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 reports^{5–7} 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).

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. Hydrogen concentrations in each collected sample were measured with a breath-hydrogen analyzer (EC60 Gastrolyzer Breath Hydrogen Monitor; Bedford Scientific, Upchurch, Kent, UK). 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. Bioptic samples are not routinely obtained from duodenal bulb, but are performed in case of micronodular bulbs (an endoscopic finding suspected for celiac disease). Obviously, bioptic 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.⁹

Celiac disease was defined as permanent gluten-sensitive enteropathy, primarily expressed by the presence of characteristic small intestinal lesions.¹⁰ 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 Oberhuber¹¹: 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.¹¹

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 show 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).⁴⁻⁷ 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 points 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

Sex	Age (yrs)	Localization of CD	Duodenal Endoscopic Feature	Marsh Lesion	AGA	EMA	Anti-tTG	Sorbitol H ₂ -BT
Male	33	Ileo-colonic	Granular aspect of second portion	IIIb	Positive	Positive	Positive	Positive
Female	20	Colonic	Scalloping of duodenal folds	IIIa	Positive	Negative	Positive	Positive
Female	43	Ileal	Absence of duodenal folds	IIIc	Positive	Positive	Positive	Positive
Male	53	Ileo-colonic	Absence of duodenal folds	IIIc	Positive	Positive	Positive	Positive
Female	53	Ileo-colonic	Reduction of duodenal folds	IIIb	Negative	Positive	Positive	Positive

- 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,¹² who described AGA positivity in about 16% of patients affected by CD.
- Despite recent data described by Datele et al¹² and Bizzarro et al,¹³ 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.¹⁴
- 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.^{9,15,16}

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 supply at low dose and concentration to patients with celiac disease resulted in an increased excretion of H₂ with respect to healthy controls.¹⁷ At the same time, it has recently been shown that this test may be useful as a screening tool in patients with celiac disease,¹⁸ and we showed more recently its effectiveness in detecting histologic lesions in patients affected by the subclinical/silent form of celiac disease.¹⁹ This study confirms the effectiveness of sorbitol H₂-BT in detecting small bowel histologic damage (it was positive in all patients affected by CD and celiac disease), but it was also positive in 4/20 (20%) patients affected by CD alone (3 patients with ileal and 1 with ileo-colonic localization); therefore, this study also confirmed the low specificity of this test in detecting small bowel histologic damage, because it did not differentiate between causes of intestinal damage.²⁰

The third point is represented by the endoscopic results. This study confirms that endoscopic markers show high

positive predicting value in diagnosing celiac disease.^{9,21} However, a recent study by Culliford et al²² described some cases of duodenal CD mimicking endoscopic aspects of celiac disease. Our study failed to show duodenal endoscopic damage related to CD and not to celiac disease: the data by Culliford et al²² should, however, be kept in mind, because the endoscopic duodenal appearance could be confounding data for an inexperienced endoscopist.

However, the very interesting data from this study are represented by the very high prevalence of celiac disease in patients affected by CD (25.92%). Why is there such a high association between these 2 diseases? We cannot forget that literature has described both cases of CD associated with celiac disease and cases of familial occurrence of inflammatory bowel disease in celiac disease.²³

We think that the immunopathogenesis of both the diseases may explain this, in particular that intraepithelial T cells may be the key to explain this. 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 (T_H1: stimulation of type 1 immunity, which is characterized by intense phagocytic activity, but also stimulates moderate levels of antibodies production) or type 2 (T_H2: 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 T_H1 pathway,²⁴ and both CD and celiac disease are characterized by a decreased cellular apoptosis, which provokes a chronic inflammation, especially in the lamina propria.²⁵ This alteration is confirmed by caspase 8 reduction²⁶ and under expression of BAX, which favors apoptosis resistance of intraepithelial T cells, as described both in CD and celiac disease.^{27,28} 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.^{29–31} Moreover, other cytokines involved in cell-mediated

immunopathogenesis [such as tumor necrosis factor α (TNF α), 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-DQ8,³³ 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 TNF α 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 enable them, thanks to an increase of the cytokine network (IL-15, IL-2, TNF α , interferon γ), to cause a T_H1 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_H1 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

- Keighley MR, Stockbrugger RW. Inflammatory bowel disease. *Aliment Pharmacol Ther.* 2003;18(suppl 3):66–70.
- Martucci S, Biagi F, Di Sabatino A, et al. Coeliac disease. *Dig Liver Dis.* 2002;34(suppl 2):S150–S153.
- Catassi C, Ratsch IM, Fabiani E, et al. Coeliac disease in the year 2000: exploring the iceberg. *Lancet.* 1994;343:200–203.
- Tursi A, Giorgetti GM, Brandimarte G, et al. Prevalence and clinical presentation of subclinical/silent coeliac disease in adults: an analysis on a 12-year observation. *Hepatogastroenterology.* 2001;39:462–464.
- Cheikh I, Maamouri N, Chouaib S, et al. Association of celiac disease and Crohn's disease. A case report. *Tunis Med.* 2003;81:969–971.
- Chakraborty A, Bremner AR, Moore I, et al. Coeliac disease and Crohn's disease: an association not to be forgotten. *Hosp Med.* 2003;64:684–685.
- Schedel J, Rockmann F, Bongartz T, et al. Association of Crohn's disease and latent celiac disease: a case report and review of the literature. *Int J Colorectal Dis.* 2004.
- Kornbluth A, Salomon P, Sachard DB. Crohn's disease. In: Sleisenger MH, Fordtrand JS, eds. *Gastrointestinal Disease.* 5th ed. Philadelphia, PA: WB Saunders, 1993:1270–1304.
- Tursi A, Brandimarte G, Giorgetti GM, et al. Endoscopic features of coeliac disease in adults and its correlation with age, histological damage and clinical form of the disease. *Endoscopy.* 2002;34:787–792.
- Feighery C, Weir DG, Whelan A, et al. Diagnosis of gluten-sensitive enteropathy: is exclusively reliance on histology appropriate? *Eur J Gastroenterol Hepatol.* 1998;10:919–925.
- Oberhuber G, Grandisch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol.* 1999;11:1185–1194.
- Datele AV, Aldhous MC, Humphreys K, et al. Serum tissue anti-transglutaminase antibodies in coeliac disease and other gastrointestinal disease. *Q J Med.* 2001;94:195–205.
- Bizzarro N, Villalta D, Tonutti ER, et al. IgA and IgG tissue transglutaminase antibody prevalence and clinical significance in connective tissue diseases, inflammatory bowel disease, and primary biliary cirrhosis. *Dig Dis Sci.* 2003;48:2360–2365.
- Sblattero D, Berti I, Trevisiol C, et al. Human recombinant tissue transglutaminase ELISA: an innovative diagnostic assay for celiac disease. *Am J Gastroenterol.* 2000;95:1253–1257.
- Tursi A, Brandimarte G, Giorgetti GM, et al. Low prevalence of anti-gliadin (AGA) and anti-endomysium (EMA) antibodies in subclinical/silent celiac disease. *Am J Gastroenterol.* 2001;96:1507–1510.
- Abrams JA, Diamone B, Rotterdam H, et al. Seronegative celiac disease: increased prevalence with lesser degrees of villous atrophy. *Dig Dis Sci.* 2004;49:546–550.
- Corazza GR, Strocchi A, Rossi R, et al. Sorbitol malabsorption in normal volunteers and in patients with coeliac disease. *Gut.* 1988;29:44–48.
- Pelli MA, Capodicasa E, De Angelis V, et al. Sorbitol H₂-breath test in celiac disease. Importance of early positivity. *Gastroenterol Int.* 1998;11:65–68.
- Tursi A, Brandimarte G, Giorgetti GM. Sorbitol H₂-breath test versus anti-endomysium (EMA) antibodies for the diagnosis of subclinical/silent coeliac disease. *Scand J Gastroenterol.* 2001;36:1170–1172.
- Tursi A, Brandimarte G, Giorgetti GM. H₂ breath tests for the diagnosis of celiac disease. *Am J Gastroenterol.* 2002;97:2679–2680.
- Brocchi E, Tomassetti P, Misitano B, et al. Endoscopic markers in adult coeliac disease. *Dig Liver Dis.* 2002;34:177–182.
- Culliford A, Markowitz D, Rotterdam H, et al. Scalping of duodenal mucosa in Crohn's disease. *Inflamm Bowel Dis.* 2004;10:270–273.
- Cottone M, Marrone C, Casa A, et al. Familial occurrence of inflammatory bowel disease in celiac disease. *Inflamm Bowel Dis.* 2003;9:321–323.
- Cominelli F. Cytokine-based therapies for Crohn's disease—new paradigms. *N Engl J Med.* 2004;351:2045–2048.
- Levine AD, Fiocchi C. Regulation of life and death in lamina propria cells. *Immunology.* 2001;13:195–199.
- Sturm A, Mohr S, Fiocchi C. Critical role of caspases in the regulation of apoptosis and proliferation of mucosal T cells. *Gastroenterology.* 2002;122:1334–1345.
- Itoh J, De La Motte C, Strong SA, et al. Decreased BAX expression by mucosal T cells favours resistance to apoptosis in Crohn's disease. *Gut.* 2001;49:35–41.
- Chermarsky AC, Rubio AF, Vanzulli S, Rubinstein N, De Rosa D, Fain boim L. Evidences of the involvement of Bak, a member of the Bcl-2 family proteins, in active coeliac disease. *Autoimmunity.* 2002;35:29–37.
- Liu Z, Geboes K, Colpaert S, et al. IL-15 is highly expressed in inflammatory bowel disease and regulates local T cell-dependent cytokine production. *J Immunol.* 2000;164:3608–3615.
- Maiuri L, Ciacci C, Vacca L, et al. IL-15 drives the specific migration of CD94+ and TCR- γ delta+ intraepithelial lymphocytes in organ cultures of treated celiac patients. *Am J Gastroenterol.* 2001;96:150–156.
- Meresse B, Chen Z, Ciszewski C, et al. Coordinated induction by IL15 of a TCR-independent NKG2D signalling pathway converts CTL into lymphokine-activated K cells in celiac disease. *Immunity.* 2004;21:357–366.

32. Jelinkova L, Tuckova L, Cinova J, et al. Gliadin stimulates human monocytes to production of IL-8 and TNF-alpha through a mechanism involving NF-kappaB. *FEBS Lett.* 2004;571:81-85.
33. Tursi A. The genetic puzzle of celiac disease. *Gastroenterology.* 2004;126:1216-1217.
34. Yap LM, Ahmad T, Jewell DP. The contribution of HLA genes to IBD susceptibility and phenotype. *Best Pract Res Clin Gastroenterol.* 2004;18:577-596.
35. Gibson PR. Increased gut permeability in Crohn's disease: is TNF the link? *Gut.* 2001;53:1724-1725.
36. Tursi A. Clinical implications of delayed orocecal transit time and bacterial overgrowth in adult patients with Crohn's disease. *J Clin Gastroenterol.* 2001;32:274-275.
37. Fasano A, Not T, Wang A, et al. Newly discovered modulator of intestinal permeability and its expression in celiac disease. *Lancet.* 2000;335:1518-1519.
38. Barta Z, Csí Pö I, Szabó GG, et al. Seroreactivity against *Saccharomyces cerevisiae* in patients with Crohn's disease and celiac disease. *World J Gastroenterol.* 2003;9:2308-2312.