European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2006; 10: 127-130

Crohn's disease and celiac disease: association or epiphenomenon?

A. TURSI, G.M. GIORGETTI*, G. BRANDIMARTE**, W. ELISEI**

Digestive Endoscopy Unit, "Lorenzo Bonomo" Hospital – Andria, BA (Italy)
*Department of Internal Medicine, Clinical Nutrition Unit, "S. Eugenio" Hospital – Rome (Italy)
**Department of Internal Medicine, Division of Gastroenterology, "Cristo Re" Hospital – Rome (Italy)

Abstract. – Recent literature data show a certain relation between Crohn's disease and celiac disease. We describe herein what are the pro and the cons about a possible association between Crohn's disease and celiac disease.

Key Words:

Celiac disease, Crohn's disease.

Introduction

Crohn's disease is a chronic inflammatory disease of bowel potentially affecting mainly 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[2].

Celiac disease is a malabsorption syndrome caused by gluten-induced small intestinal damage. It is characterized by a flattened mucosa, villous atrophy and crypt hyperplasia in the small intestine and by malabsorption syndrome (diarrhea, steatorrhea, weight loss) or by minor apparently unrelated symptoms such as iron-deficiency anaemia, osteopenic bone disease, amenorrhea and infertility[1]. The lack of gluten in the diet generally leads to a return to normality of the morphological changes[3].

Some recent case reports[4-7] showed that there is a certain relation between Crohn's disease and celiac disease. These data have been recently confirmed by an our prospective study: about 18% of patients affected by Crohn's disease are also affected by celiac disease[8].

But why there is a so strict relation? It is a real association or celiac disease-like lesions in Crohn's disease should be considered as epiphenomenon?

Why to Investigate About Celiac Disease in Crohn's Disease?

Diagnosis of celiac disease is often incidental. It is a common finding in clinical practice that in some cases of non-stenotic, non-fistulizing Crohn's disease it is quite difficult to obtain adequate control of diarrhoea, despite exclusion of the most frequent causes of diarrhoea (as parasitic infestations or *Clostridium difficile* infection due to long-course of antibiotics). In fact, in most of cases reported the diagnosis of celiac disease in Crohn's disease was due to not reversible diarrhea after an anti-inflammatory therapy had started[4-7]. In light of these studies, we think that celiac disease should be always investigated in Crohn's disease as soon as possible.

How to Investigate About Celiac Disease in Crohn's Disease

The first problem in clinical practice is how to investigate about celiac disease in Crohn's disease. This is an important point, since most of the common tests in screening celiac disease often fail (both as false positive and as false negative).

Corresponding Author: Antonio Tursi, MD; e-mail: antotursi@tiscali.it

Serological Tests

- Anti-gliadin antibodies (AGA) show poor specificity, since AGA can be found in 14-16% of patients affected by Crohn's disease (and in absence of celiac disease)[8].
- Anti-endomysium antibodies (EMA) seem to be more interesting for high sensitivity and specificity. However, it need technical expertise lecture and the recent data about their low prevalence in clinical practice[9] seems to limit their use as screening test in Crohn's disease.
- Also anti-tissue transglutaminase (tTG) antibodies seem to be not useful. We found contrasting results in this field. In fact we found some cases of IBD patients showing anti-tTG positivity but not affected by celiac disease (personal communication), in line to other literature experiences[10,11]. On the other hand, we also failed to find anti-tTG in patients affected by Crohn's disease and celiac disease[8]. Two different hypotheses may be made about this. First of all, this results may be in part related to the different diagnostic assay in assessing anti-tTG (human recombinant anti-tTG versus guinea pig liver anti-tTG)[12]. Second, the presence of anti-tTG in Crohn's disease patients may be a consequence of the induction of an increased apoptosis in those regions undergoing the destruction typical of severe celiac disease-associated lesions, that is a common event in every chronic gastrointestinal disease[13].
- Several patients affected by Crohn's disease and celiac disease are seronegative for AGA, EMA and anti-tTG. This is particularly true for patients showing slight/moderate histological damage of duodenum (Marsh II-IIIa lesions)[14,15].

Sorbitol H_2 Breath Test

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, since its supply at low dose and concentration to patients with celiac disease resulted in an increased excretion of H_2 with respect to healthy controls[16]. It has been recently showed that this test may be useful as a screening tool in patients with celiac disease[17], as well as we demonstrate its effectiveness also in detecting histological lesions in the patients affected by subclinical/silent form[18]. Unfortunately, we found sorbitol H_2-BT effective in detecting small bowel histological damage both in Crohn's disease and celiac disease: so, we confirmed the low specificity of this test in detecting small bowel histological damage, since it did not differentiate between the causes of intestinal damage[19].

Endoscopy

Endoscopic markers show an high positive predicting value in diagnosing celiac disease[14,20]. However, recently Culliford et al described some cases of duodenal Crohn's disease mimicking the endoscopic aspects of celiac disease[21]. We failed to find duodenal endoscopic damage related to Crohn's disease and not to celiac disease: the data by Culliford et al should be thus kept in mind, since the only endoscopic duodenal appearance could be a confounding data for a not expert endoscopist.

Celiac Disease in Crohn's Disease: Immuno-Pathogenetic Hypothesis

We think that the immuno-pathogenesis of both the diseases and in particular intraepithelial T cells may be the key to explain this association. The human gastrointestinal tract possesses a complex echosystem, in which there is a correct balance between antigenic stimuli and immune response. Chronic inflammatory intestinal disease are characterized by an up-regulation of the immunological response, which may be T helper type 1 (Th1: stimulation of type 1 immunity, which is characterized by intense phagocytic activity, and moderate stimulation of antibodies) or type 2 (Th2: stimulation of type 2 immunity, which is characterized by suppression of phagocytic activity and high antibodies titers) immunologic response. Both Crohn's disease and celiac disease are related to Th1 pathway[22], characterized by a decreased cellular apoptosis, which provoke a chronic inflammation especially in the lamina propria[23]. This alteration is confirmed by caspase 8 reduction[24] and under expression of BAX which favors apoptosis resistance of intraepithelial T cells, as described in both these diseases[25,26]. These findings seem to be related to IL-15 action. This cytokine shares biological

activities but no significant sequence homology with IL-2; it induces T cell recruitment to site of inflammation, T cell proliferation, cytokines production and rescue from apoptosis. IL-15 over-expression has been also demonstrated[27-29]. Moreover, other cytokines involved in cell-mediated immuno-pathogenesis (such as TNF-α, INF-γ or IL-8) are increased in both diseases[22,30]. All these data confirm the possible common immuno-pathogenesis of both diseases.

Why not all Crohn's disease patients develop celiac disease? The first hypothesis is that these diseases show different HLA susceptibility. We know the strict relation between celiac disease and HLA-DQ2 and HLA-DQ8[31], while the relation between Crohn's disease and HLA genes seems to be lacking[32]. So, only Crohn's disease patients showing HLA-DQ2 or –DQ8 could develop then also the celiac disease. Another more intriguing hypothesis is related to the increased gut permeability in these diseases. Crohn's disease is characterized by an increased gut permeability, which may be related to TNF-α action[33], and it may provoke a bacterial translocation as consequence of the bacterial overgrowth[34]. Also the celiac disease shows an increased gut permeability due to zonulin reduction, a protein modeling intestinal permeability between tight junctions[35]. The hypothesis explaining this association may be the follows: the increased permeability in Crohn's disease may expose several bacteria mimicking the 57-68 and/or 62-75 gliadin sequence, and able then, thanks to increasing of cytokines network (IL-15, Il-2, TNF-α, INF-γ), to cause a Th1 immunological reaction with development of celiac disease lesions. This hypothesis seems confirmed by the recent demonstration of high seroreactivity against *Saccharomyces cerevisiae* not only in Crohn's disease but also in celiac disease[36]. It is then possible that specific alimentary and/or bacterial antigens may cause celiac disease in patients affected by Crohn's disease thanks to Th1 pathway.

In conclusion, Crohn's disease shows a strict correlation with celiac disease. This association should kept in mind when we diagnose a new case of Crohn's disease. More accurate immunopathological studies should be performed to explain whether there is a common immunopathogenesis in both diseases.

References

1) Martucci S, Biagi F, Di Sabatino A, Corazza GR. Coeliac disease. Digest Liver Dis 2002; 34 (Suppl. 2): S150-S153.

2) Keighley MR, Stockbrugger RW. Inflammatory bowel disease. Aliment Pharmacol Ther 2003; 18 (Suppl. 3): 66-70.

3) Catassi C, Ratsch IM, Fabiani E, Rossigni M, Mordicchia F, Candela F, Coppa GV, Giorgi PL. Coeliac disease in the year 2000: exploring the iceberg. Lancet 1994; 343: 200-203.

4) Tursi A, Giorgetti GM, Brandimarte G, Rubino E, Lombardi D, Gasbarrini G. Prevalence and clinical presentation of subclinical/silent coeliac disease in adults: an analysis on a 12-year observation. Hepato-Gastroenterol 2001; 39: 462-464.

5) Cheikh I, Maamouri N, Chouaib S, Chaabouni H, Ouerghi H, Ben Ammar A. Association of celiac disease and Crohn's disease. A case report. Tunis Med 2003; 81: 969-971.

6) Chakraborty A, Bremner AR, Moore I, Beattie RM. Coeliac disease and Crohn's disease: an association not to be forgotten. Hosp Med 2003; 64: 684-685.

7) Schedel J, Rockmann F, Bongartz T, Woenckhaus M, Scholmerich E, Kullmann F. Association of Crohn's disease and latent celiac disease: a case report and review of the literature. Int J Colorectal Dis 2005; 20: 376-380.

8) Tursi A, Giorgetti GM, Brandimarte G, Elisei W. High prevalence of celiac disease among patients affected by Crohn's disease. Inflamm Bowel Dis 2005; 11: 662-666.

9) Tursi A, Brandimarte G, Giorgetti GM, Gigliobianco G, Lombardi D, Gasbarrini G. Low prevalence of antigliadin (AGA) and anti-endomysium (EMA) antibodies in subclinical/silent celiac disease. Am J Gastroenterol 2001; 96: 1507-1510.

10) Bizzarro N, Villalta D, Tonutti E, Doria A, Tampoia M, Bassetti D, Tozzoli R. 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.

11) Datele AVM, Aldhous MC, Humphreys K, Ghosh S. Serum tissue anti.transglutaminase antibodies in coeliac disease and other gastrointestinal disease. Q J Med 2001; 94: 195-205.

12) Sblattero D, Berti I, Trevisiol C, Marzari R, Tommasini A, Bradbury A, Fasano A, Not T. Human recombinant tissue transglutaminase ELISA: an innovative diagnostic assay for celiac disease. Am J Gastroenterol 2000; 95: 1253-1257.

13) Farrace MG, Picarelli A, Di Tola M, Sabbatella L, Marchione OP, Ippolito G, Piacentini M. Presence of anti-"tissue" transglutaminase antibodies in inflammatory intestinal diseases: an apoptosis-associated event? Cell Death Differ 2001; 8: 767-770.

14) Tursi A, Brandimarte G, Giorgetti GM, Gigliobianco A. 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.

15) Abrams JA, Diamone B, Rotterdam H, Green PHR. Seronegative celiac disease: increased prevalence with lesser degrees of villous atrophy. Dig Dis Sci 2004; 49: 546-550.

16) Corazza GR, Strocchi A, Rossi R, Sirola D, Gasbarrini G. Sorbitol malabsorption in normal volunteers and in patients with coeliac disease. Gut 1988; 29: 44-48.

17) Pelli MA, Capodicasa E, De Angelis V, Morelli A, Bassotti G. Sorbitol H2-breath test in celiac disease. Importance of early positivity. Gastroenterol Int 1998; 11: 65-68.

18) Tursi A, Brandimarte G, Giorgetti GM. Sorbitol H2-Breath test versus anti-endomysium (EMA) antibodies for the diagnosis of subclinical/silent coeliac disese. Scand J Gastroenterol 2001; 36: 1170-1172.

19) Tursi A, Brandimarte G, Giorgetti GM. H2 breath tests for the diagnosis of celiac disease. Am J Gastroenterol 2002; 97: 2679-2680.

20) Brocchi E, Tomassetti P, Misitano B, Epifanio G, Corinaldesi R, Bonvicini F, Gasbarrini G, Corazza G. Endoscopic markers in adult coeliac disease. Dig Liver Dis 2002; 34: 177-182.

21) Culliford A, Markowitz, Rotterdam H, Green PH. Scalloping of duodenal mucosa in Crohn's disease. Inflamm Bowel Dis 2004; 10: 270-273.

22) Cominelli F. Cytokine-based therapies for Crohn's disease–new paradigms. N Engl J Med 2004; 351: 2045-2048.

23) Levine AD, Fiocchi C. Regulation of life and death in lamina propria cells. Immunology 2001; 13: 195-199.

24) 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.

25) Itoh J, De La Motte C, Strong SA, Levine AD, Fiocchi C. Decreased BAX expression by mucosal T cells favours resistance to apoptosis in Crohn's disease. Gut 2001; 49: 35-41.

26) Chernavsky AC, Rubio AE, Vanzulli S, Rubinstein N, De Rosa S, Fainboim L. Evidences of the involvement of Bak, a member of the Bcl-2 family proteins, in active coeliac disease. Autoimmunity 2002; 35: 29-37.

27) Liu Z, Geboes K, Colpaert S, D'Haens GR, Rutgeers P, Ceuppens JL. IL-15 is highly expressed in inflammatory bowel disease and regulates local T cell-dependent cytokine production. J Immunol 2000; 164: 3608-3615.

28) Maiuri L, Ciacci C, Vacca L, Ricciardielli I, Auricchio S, Quarantino S, Londei M. IL-15 drives the specific migration of CD94+ and TCR- gammadelta+ intraepithelial lymphocytes in organ cultures of treated celiac patients. Am J Gastroenterol 2001; 96: 150-156.

29) Meresse B, Chen Z, Ciszewski C, Tretiakova M, Bhagat G, Krausz TN, Raulet DH, Lanier LL, Groh V, Spies T, Ebert EC, Green PH, Jabri B. 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.

30) Jelinkova L, Tuckova L, Cinova J, Flegelova Z, Tlaskalova-Hogenova H. Gliadin stimulates human monocytes to production of IL-8 and TNF-alpha through a mechanism involving NF-kappaB. FEBS Lett 2004; 571: 81-85.

31) Tursi A. The genetic puzzle of celiac disease. Gastroenterology 2004; 126: 1216-1217.

32) 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.

33) Gibson PR. Increased gut permeability in Crohn's disease: is TNF the link? Gut 2001; 53: 1724-1725.

34) 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.

35) Fasano A, Not T, Wang A, et al. Zonulin A: newly discovered modulator of intestinal permeability and its expression in celiac disease. Lancet 2000; 335: 1518-1519.

36) Barta Z, Csipo I, Szabo GG, Szegedi G. Seroreactivity against Saccharomyces cerevisiae in patients with Crohn's disease and celiac disease. World J Gastroenterol 2003; 9: 2308-2312.