Association between celiac disease and Crohn's disease - a challenge to the coloproctologist

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Especial

Association between celiac disease and Crohn's disease – a challenge to the coloproctologist

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ABSTRACT: Over the past few years, many studies on the association between celiac disease and inflammatory bowel disease have been reported. The genetic origin of this association has prompted research that searches for a common link for the concomitant manifestation of these pathologies. Clinical studies aim not only to demonstrate this relation, but also to establish the epidemiological frequencies among affected individuals and their relatives as compared to the general population. The similar clinical symptoms, difficulties, diagnoses, and therapeutics are still a challenge, since this association is unknown to most coloproctologists, thereby culminating in treatments and surgical procedures with no benefits for the patient.

Keywords: celiac disease; Crohn's disease; proctocolitis; association.

RESUMO: Nos últimos anos, muitos estudos foram relatados sobre a associação entre a doença celíaca e as doenças inflamatórias intestinais. A origem genética dessa associação desperta pesquisas que buscam o elo comum para a manifestação concomitante das patologias. Estudos clínicos visam não apenas demonstrar essa relação mas também estabelecer as frequências epidemiológicas entre os indivíduos acometidos e seus familiares em relação à população geral. À semelhança do quadro clínico, as dificuldades diagnósticas e terapêuticas são ainda desafios, já que tal associação ainda é desconhecida para a maioria dos coloproctologistas, podendo resultar em tratamentos e cirurgias sem benefícios ao paciente.

Palavras-chave: doença celíaca; doença de Crohn; proctocolite; associação.

INTRODUCTION

The celiac disease (CD) is characterized as an autoimmune disease caused by the permanent gluten intolerance in genetically susceptible individuals[1]. In the past few years, its clinical and ethiopathogenic features have been cleared. Nowadays, it is known that in order for it to occur the association of three factors is determinant: genetic changes, exposure to gluten and altered immune response[3].

Histocompatibility antigens class II, HLA-DQ2 and HLA-DQ8 present changes in celiac patients[3-5]. When these subjects are exposed to gluten, their immune response is exaggerated, with increase in intraepithelial T lymphocytes – in the proximal intestine mucosa – and inflammatory cytokines, leading to the villous atrophy and poor absorption of nutrients[6]. Excluding gluten from the diet usually leads to the regression of morphological changes in the proximal intestine[7]. Such changes result in the

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clinical variants of the disease and its intensity, so the onset of early symptoms can occur during childhood or adulthood[8,9]. Thus, CD fits the differential diagnosis of other pathologies that present pain and abdominal distension, vomit, iron deficiency and malnutrition[10].

In adult subjects, the diagnosis of CD should include detailed anamnesis, serological and histopathological studies[11]. However, in this age group the disease can be subclinical, and diagnosis can be late – sometimes, after surgical approaches, since it seems like a picture of acute abdomen, or after other therapies that provided no benefits to the patient[12,13]. The immunological characteristics of CD establish a relation with other autoimmune conditions, such as dermatitis herpetiformis, thyroid diseases, Addison's disease, autoimmune thrombocytopenia, sarcoidosis, IgA nephropathy and selective IgA deficiency[14-16]. Approximately 2 to 4% of the insulin dependent patients with diabetes mellitus present with CD[17].

The relation with other autoimmune diseases led to studies on the association between CD and inflammatory bowel diseases (IBD) in the past few years (proctocolitis and Crohn's disease)[18-21].

Crohn's disease is more common in the terminal ileum. It presents segmental lesions in the digestive tract, affecting all the layers of the organ wall and possibly leading to stenosis or fistula. Proctocolitis is the IBD more commonly associated with other autoimmune diseases, such sclerosing cholangitis, and other vasculitis. Anemia and malnutrition are systemic repercussions that are present in most patients with the disease. The iron-deficiency anemia, which is refractory in patients with IBD, should lead to the suspicion of associated CD[22].

Many clinical studies and case reports have been described in the past few years to relate CD and IBD. The prevalence of IBD in CD has been described as five to ten times higher in the general population[23]. Shah et al. described a risk of proctocolitis five times higher relative in first-degree relatives of patients with CD[24]. Likewise, Cottone et al. described the high incidence of proctocolitis in 600 first-degree relatives of patients with CD[25].

Between January 2002 and December 2004, the Italian Group of Inflammatory Bowel Diseases performed a multicentric study aiming to establish the prevalence of IBD among celiac patients. Out of the 1,711 patients, 9 (0.5%) serological and histological results that were compatible with the CD diagnosis – 6 patients presented with proctocolitis and three with Crohn's disease, lower prevalence in comparison to the general population[26].

In 2007, during 1 year period, Masachs et al. followed-up three groups of celiac patients, their first-degree relatives and a control group, in order to identify the prevalence of IBD in celiac patients and their relatives. Three cases of Crohn's disease were reported in 86 celiac patients; four cases of Crohn's disease in first-degree relatives; and one case in the control group (809 people); no case of proctocolitis was reported, which led to the conclusion that celiac patients and their first-degree relatives have higher chances of having Crohn's disease if compared to the general population[27].

Lopez-Vasquez et al. identified mutations in the A MICA gene (major histocompatibility complex class I chain related gene A) expressed in the gastrointestinal epithelium of patients with IBD[28]. Changes in the MYOIXB gene, responsible for the production of myosins and for the intestinal epithelial integrity, are found in celiac patients[29] and these mutations can also be found in 40% of the patients with IBD[30,31].

The presence of binding regions shared by these diseases, such as 5q31-33 (IBD5 and CELIAC2) and 19p13 (IBD6 and CELIAC4)[32,33] has supported this idea. Recently, the description of polymorphisms in the genes IL2, region IL21, in 4q27 and in the gene IL18RAP, in 2q12, reinforces the evidence of association between CD and IBD. Besides, the well established relation between Crohn's disease and the gene IL23R[34] has been associated to CD in the Finn[35] and Spanish[36] population. Based on these findings, Dema et al.37 studied the genes NKX2-3, IRGM and ATG16L1, whose changes are clearly defined in the IBDs, in patients with CD and first-degree relatives; however, no evidence has been established among celiac patients.

In the service of *Hospital das Clínicas de Ribeirão Preto* (HCRP) at *Universidade de São Paulo*, we had a case of association between CD and Crohn's disease. The patient was 37 years old at the time, and in the first appointment she presented with history of

pain and abdominal distension, vomit, weight loss (10 kg in 3 months) and refractory anemia to treatments prescribed in other medical services.

There had been an intestinal subocclusion (referring to enterectomy), however, there were no reports concerning the removed piece. She had the report of an upper digestive endoscopy (UDE) with a duodenal biopsy compatible with CD. However, up until then she had not been advised to rule out gluten from her diet. We repeated the UDE with new biopsies of the second part of the duodenum, and the CD diagnosis was confirmed. Admitted to our nursery for clinical and nutritional rehabilitation, her picture of intestinal occlusion got worse, and traffic demonstrated areas of stenosis and dilatation of the small intestine (Figure 1). After being submitted to exploratory laparotomy, segments of the jejunum and ileum were shown with stenosis and dilatation (Figure 2). The exploration of the surgical piece demonstrated an inflammatory infiltrate in the mesentery, intestinal wall thickening with ulcers and fibrin deposition (Figures 3 and 4). The surgical piece was analyzed twice at the Department of Pathological Anatomy at HCRP and the diagnosis of Crohn's disease was confirmed. At the postoperative, we initiated nutritional guidance and suspended gluten from the diet. Thirty days after the surgery, we started treating the patient for Crohn's disease. An immunomodulator was prescribed and, nowadays, the patient had significant clinical improvement, without new intercurrences.

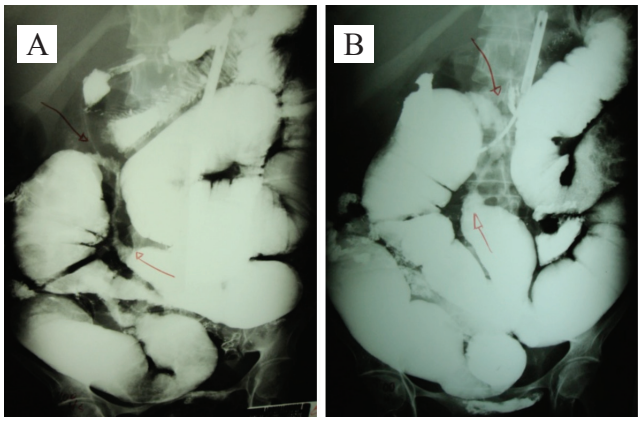

***Figure 1**. Bowel transit showing areas of stenosis and small intestine dilatation.*

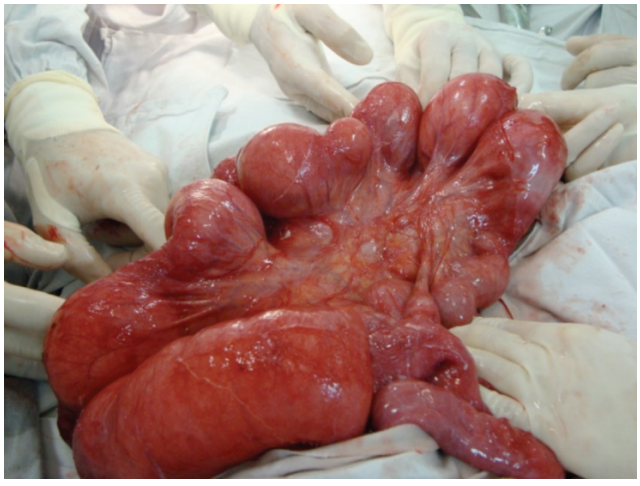

***Figure 2**. Stenoses and dilatations.*

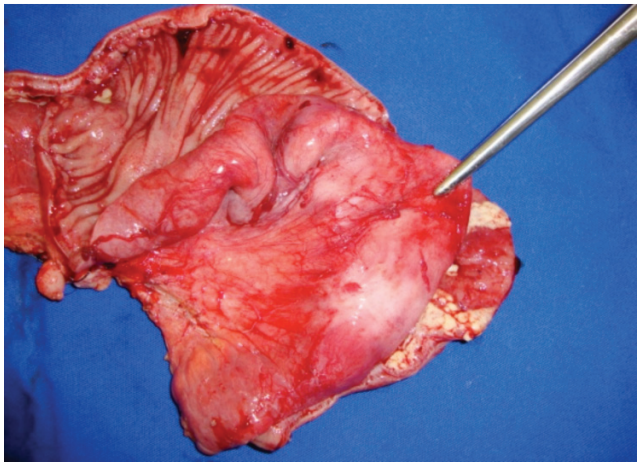

***Figure 3**. Inflammatory infiltrate in the mesentery.*

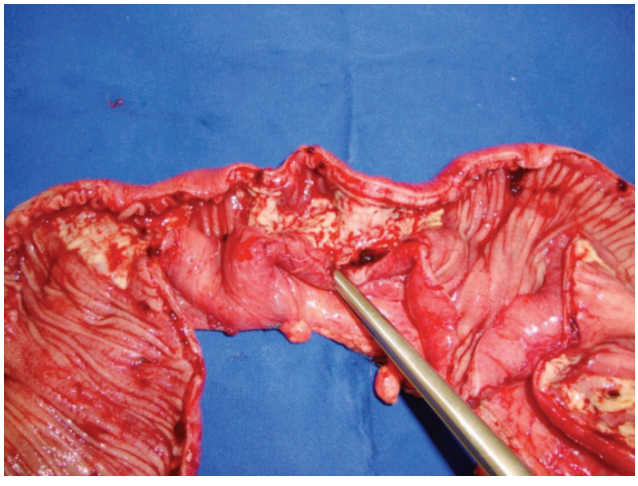

***Figure 4**. Ulcers and fibrin deposition.*

CONCLUSION

In the past few years, with the advances in diagnostic methods and molecular evaluations, the analysis between diseases whose ethiopathogens involve genetic changes and autoimmune mechanisms has improved. Thus, we can cite the studies that tried to relate CD and IBDs. It is important to remember that similarities are not restricted to genetics and immunology, because their similar clinical pictures can lead to diagnostic mistakes and incorrect treatments. The association of both pathologies in the same patient should be brought up in cases of severe malnutrition and refractory anemia to treatment. However, even though most clinical studies demonstrate this association, we are still waiting for the description of the real genetic link between these pathologies.

REFERENCES

1. Troncone R, Bhatnagar S, Butzner D, Cameron D, Hill I, Hoffenberg E, Maki M, Mendez V, de Jimenez MZ; European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Celiac disease and other immunologically mediated disorders of the gastrointestinal tract: Working Group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2004;39 Suppl 2:S601-10.
2. Baptista ML. Doença celíaca: uma visão contemporânea. Pediatria (São Paulo) 2006;28(4):262-71.
3. Ciclitira PJ, King AL, Fraser JS. AGA technical review on Celiac Sprue. American Gastroenterological Association. Gastroenterol 2001;120(6):1526-40. Erratum in: Gastroenterology 2001;121(1):234. Comment in: Gastroenterology. 2002;122(1):246-7.
4. Farré C, Humbert P, Vilar P, Varea V, Aldeguer X, Carnicer J, et al. Serological markers and HLA-DQ2 haplotype among first-degree relatives of celiac patients. Catalonian Coeliac Disease Study Group. Dig Dis Sci 1999;44(11):2344-9.
5. Sollid LM, Thorsby E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. Gastroenterology 1993;105(3):910-22.
6. Sollid LM. The molecular basis of coeliac disease. Annu Rev Immunol 2000;18:53-81.
7. Stern M, Ciclitira PJ, van Eckert R, Feighery C, Janssen FW, Méndez E, et al. Analysis and clinical effects of gluten in coeliac disease. Eur J Gastroenteol Hepatol 2001;13(6):741-7.
8. Martucci S, Biagi F, Di Sabatino A, Corazza GR. Coeliac disease. Digest Liver Dis 2002;34 Suppl 2:S150-3.
9. Catassi C, Rätsch IM, Fabiani E, Rossini M, Bordicchia F, Candela F, et al. Coeliac disease in the year 2000: exploring the iceberg. Lancet 1994;343(8891):200-3.
10. Polanco I. Enfermedad celíaca. Pediatria Integral 1995;1(2):124.
11. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: An evolving spectrum. Gastroenterol 2001;120(3):636-51.
12. Logan Rf, Rifkind EA, Turner ID, Ferguson A. Mortality in celiac disease. Gastroenterology 1989;97(2):265-71.
13. Corrao G, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, Sategna Guidetti C, Usai P, Cesari P, Pelli MA, Loperfido S, Volta U, Calabró A, Certo M; Club del Tenue Study Group. Mortality in patients with celiac disease and their relatives: a cohort study. Lancet. 2001;358(9279):356-61.
14. Holmes GKT. Coeliac disease and type 1 diabetes mellitus – the case for screening. Diabet Med 2001;18(3):169-77.
15. Arvola T, Mustalahti K, Saha MT, Vehmanen P, Partanen J, Ashorn M. Celiac disease, thyrotoxicosis and autoimmune hepatitis in a child. J Pediatr Gastroenterol Nutr 2002;35(1):90-2.
16. Kaukinen K, Collin P, Mykkänen AH, Partanen J, Mäki M, Salmi J.. Celiac disease and autoimmune endocrinologic disorders. Dig Dis Sci. 1999;44(7):1428-33..
17. Savilahti E, Simell O, Koskimies S, Rilva A, Akerblom HK. Coeliac disease in insulin-dependent diabetes mellitus. J Pediatr. 1986;108(5 Pt 1):690-3.
18. 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(12):969-71. Article in French.
19. Chakraborty A, Bremner AR, Moore I, Beattie RM. Coeliac disease and Crohn's disease: an association not to be forgotten. Hosp Med 2003;64(11):684-5.
20. Schedel J, Rockmann F, Bongartz T, Woenckhaus M, Schölmerich J, 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(4):376-80.
21. 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(7):662-6.
22. Takei N, Mukai Y, Hasegawa Y, Suzukawa K, Nagata M, Noguchi M, et al. Refractory iron deficiency anemia as the primary clinical manifestation of celiac disease. Ann Hematol 2003;82:53.
23. Gillberg R, Dotevall G, Ahren C. Chronic inflammatory bowel disease in patients with coeliac disease. Scand J Gastroenterol 1982;17(4):491-6.
24. Shah A, Mayberry JF, Williams G, Holt P, Loft DE, Rhodes J. Epidemiological survey of coeliac disease and inflammatory bowel disease in first degree relatives of coeliac patients. Q J Med 1990;74(275):283-8.
25. Cottone M, Marrone C, Casà A, Oliva L, Orlando A, Calabrese

E, et al. Familial occurrence of inflammatory bowel disease in celiac disease. Inflamm Bowel Dis 2003;9(5):321-32.
26. Casella G, D'Incà R, Oliva L, Daperno M, Saladino V, Zoli G, Annese V, Fries W, Cortellezzi C; Italian Group – IBD. Prevalence of celiac disease in inflammatory bowel diseases: an IG-IBD multicentre study. Dig Liver Dis 2010;42(3):175-8.
27. Masachs M, Casellas F, Malagelada JR. Enfermedad inflamatoria intestinal en pacientes celíacos. Rev Esp Enferm Dig. 2007;99(8):446-50.
28. Lopez-Vazquez A, Rodrigo L, Fuentes D, Riestra S, Bousoño C, Garcia-Fernandez S, et al. MHC class I chain related gene A (MICA) modulates the development of celiac disease in patients with the high risk heterodimer DQA1 0501/DQB1 0201. Gut 2002;50(3):336-40.
29. Monsuur AJ, de Bakker PI, Alizadeh BZ, Zhernakova A, Bevova MR, Strengman E, et al. Myosin IXB variant increases the risk of celiac disease and points toward a primary intestinal barrier defect. Nat Genet 2005;37(12):1341-4.
30. van Bodegraven AA, Curley CR, Hunt KA, Monsuur AJ, Linskens RK, Onnie CM, et al. Genetic variation in myosin IXB is associated with ulcerative colitis. Gastroenterology 2006;131(6):1768-74.
31. Latiano A, Palmieri O, Valvano MR, D'Incà R, Caprilli R, Cucchiara S, et al. The association of MYO9B gene in Italian patients with inflammatory bowel diseases. Aliment Pharmacol Ther 2008;27(3):241-8.
32. Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, McLeod RS, Griffiths AM, et al. Genomewide search in Canadian families with inflammatory bowel disease reveals two novel susceptibility loci. Am J Hum Genet 2000;66(6):1863-70.
33. Van Belzen MJ, Meijer JW, Sandkuijl LA, Bardoel AF, Mulder CJ, Pearson PL, et al. A major non-HLA locus in celiac disease maps to chromosome 19. Gastroenterology 2003;125(4):1032-41.
34. Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science. 2006;314(5804):1461-3..
35. Einarsdottir E, Koskinen LL, Dukes E, Kainu K, Suomela S, Lappalainen M, et al. IL23R in the Swedish, Finnish, Hungarian and Italian populations: association with IBD and psoriasis, and linkage to celiac disease. BMC Med Genet 2009;10:8
36. Nunez C, Dema B, Cenit MC, Polanco I, Maluenda C, Arroyo R, et al. IL23R: a susceptibility locus for celiac disease and multiple sclerosis? Genes Immun 2008;9(4):289-93.
37. Dema B, Fernández-Arquero M , Maluenda C, Polanco I, Figueredo M, de la Concha EG, et al. Lack of association of NKX2-3, IRGM, and ATG16L1 inflammatory bowel disease susceptibility variants with celiac disease. Human Immunology 2009;70(11):946-9.

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