

Prevalence of Celiac Disease in Patients with Inflammatory Bowel Disease in Northeastern Brazil

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ABSTRACT

AIM: Evaluate the prevalence of celiac disease in patients diagnosed with inflammatory bowel disease followed at the General Hospital - UFPE. Celiac disease represents an autoimmune enteropathy related to gluten intolerance, causing chronic inflammation, especially of the small intestine. The typical clinical presentation is marked by disabsorptive diarrhea, abdominal distension and malnutrition. Atypical forms, however, have been increasingly documented, demonstrating that the occurrence of the disease, previously considered rare, may reach 1% of the population in some series. Some recent case reports and more recent cross-sectional studies have suggested higher prevalence of celiac disease in patients with inflammatory bowel disease.

MATERIALS AND METHODS: As screening test, anti-endomysial

al IgA antibodies were measured by indirect immunofluorescence in 83 patients with confirmed diagnosis of Crohn's disease or idiopathic ulcerative colitis, in order to select those who would be referred for duodenal biopsy.

RESULTS: No test was positive for anti-endomysial antibodies.

CONCLUSION: Despite the small number of patients evaluated, it can be suggested that there is no higher prevalence of celiac disease in patients with inflammatory bowel disease.

Key words: Celiac disease; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Antibodies

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INTRODUCTION

Celiac Disease (CD) is a precipitated autoimmune enteropathy affecting genetically predisposed individuals due to gluten intolerance, a protein fraction contained in cereals such as wheat, rye and barley^[1-3]. Gluten protein is rich in glutamine and proline peptides that are relatively resistant to gastric and pancreatic enzymes^[1,4]. Amines that make up these peptides (e.g. gliadin in wheat and hordein in barley) are responsible for lymphocyte activation and development of the immunogenic response, characterized by chronic inflammation of mucosa and submucosa mainly of the small intestine^[4].

Inflammatory bowel diseases (IBD) comprise two main forms of presentation: Crohn's Disease (CrD) and Idiopathic Ulcerative Colitis (UC). Both are immunologically mediated affections with genetic predisposition that have its main trigger in the deregulation of the immune tolerance to the intestinal microbiota. Although they show differences in the main site of occurrence and transmural extent of inflammation, they share several similarities with CD.

The clinical and immunological similarities shared by CD and

IBD aroused researchers' interest on the coexistence of these two conditions, previously dichotomically seen as differential diagnosis. In literature, studies have shown higher prevalence of IBD in first-degree relatives of celiac patients^[5,6]. Reports and case series have also suggested the association of both CrD and UC with CD^[7-10]. However, in relation to the prevalence of CD in patients with IBD, there are still many disagreements and controversies. While some authors demonstrate higher prevalence of CD in patients with IBD^[11], others rule out this possibility, suggesting a similar or even lower prevalence than in the general population^[12-14].

The aim of the present study was to analyze the prevalence of celiac disease in patients with confirmed inflammatory bowel disease followed at a reference outpatient clinic in the State of Pernambuco, northeastern Brazil, for the treatment of patients with inflammatory bowel diseases at the General Hospital of the Federal University of Pernambuco (HC -UFPE).

METHODS

Of the patients treated in the outpatient clinic of inflammatory bowel disease or hospitalized in the Gastroenterology Unit of the General Hospital - UFPE from October 31 to December 19, 2015, a total of 83 were selected and included in the study. All had CrD or UC diagnosed by means of low digestive endoscopy and confirmed by histopathological examination of endoscopic biopsy fragments.

Through peripheral venipuncture, 4ml blood samples were collected from each patient, stored in a vacuum-dried tube (VACUETTE®), centrifuged, frozen and sent to the laboratory for clinical analysis. As initial screening, the dosage of the Anti-Endomysial IgA Antibody (AAE) was measured by means of the indirect immunofluorescence technique, with the result given in titers, using cryostat cuts of monkey esophagus tissue as substrate for antibody determination, being considered positive test when at titration greater than 1: 5. Upper digestive endoscopy with biopsies of second duodenal portion to investigate histopathological alterations compatible with celiac disease would be performed to confirm the diagnosis in cases of AAE positivity.

Epidemiological data related to the patient, such as gender, age and ethnicity were evaluated. Regarding inflammatory bowel disease, the study analyzed information on the duration of the disease from diagnosis to inclusion in the study, clinical classification (i.e., proctitis, left colitis or pancolitis - in case of UC or inflammatory, stenosing or fistulizing - in case of CrD), use of medications, as well as need for systemic corticosteroids or immunobiological therapy. Clinical control was assessed through clinical scores of inflammatory activity - Montreal and Harvey-Bradshaw for UC and CrD, respectively, as well as other indicators such as increased serum inflammatory tests, persistent anemia and hypoalbuminemia despite therapy or evidence of inflammatory activity in recent endoscopic examination.

The ethics research committee of the General Hospital – UFPE, submitted the study to approval and all patients signed a free and informed consent form, authorizing the collection of peripheral blood. There were no conflicts of interest.

RESULTS

A total of 83 patients were included in the study. The age of patients ranged from 15 to 77 years (mean of 43 years), and the mean disease duration since diagnosis was 10 years, ranging from 7 months to 27 years (Table 1). Forty-seven patients (56.6%) had idiopathic ulcerative colitis and 36 (43.4%) patients had Crohn's

disease. Women and brown skin color patients comprised 68.6% (57 patients) and 67.4% (56 patients), respectively. Other data regarding the disease classification, clinical activity and use of systemic corticosteroids or immunobiological therapy are shown in table 2.

Indirect immunofluorescence assays for anti-endomysial IgA antibody were negative in all patients tested. Thus, no patient underwent upper digestive endoscopy with biopsy of the second duodenal portion.

DISCUSSION

Celiac disease was considered a rare disease that predominated in the European population, especially individuals living in the Mediterranean, and their descendants. However, recent population studies based on serological tests conducted in the United States^[15] and Latin American countries like Argentina^[16] and Brazil^[17-19] have also demonstrated a high prevalence of CD in the general population, with rates comparable to European countries, showing that it is not a disease restricted to specific population groups.

Table 1 Studied patients characteristics.

Median Age	43 (15 - 77)
Women	57 (68.7%)
Ethnic	
Caucasian	23 (27.8%)
African American	4 (4.8%)
Brown Skin	56 (67.4%)
Median disease duration	10 years (7 months - 27 years)
Inflammatory Bowel Disease	
Crohn's Disease	36 (43.4%)
Ulcerative Colitis	47 (56.6%)

Table 2 Inflammatory Bowel Disease patients characteristics

IBD Classification	
<i>Ulcerative Colitis</i>	47 (100%)
Proctitis	13 (27.6%)
Left Colitis	6 (12.7%)
Pancolitis	28 (59.5%)
<i>Crohn's Disease</i>	36 (100%)
Inflammatory	11 (30.5%)
Stenosing	10 (27.7%)
Fistulizing	15 (41.6%)
Uncontrolled Clinical Activity [44 (53%)¹]	
<i>Ulcerative Colitis</i>	20 (45.4%) ²
Proctitis	2 (4.5%)
Left Colitis	3 (6.8%)
Pancolitis	15 (34.1%)
<i>Crohn's Disease</i>	24 (54.5%) ²
Inflammatory	5 (11.4%)
Stenosing	8 (18.1%)
Fistulizing	11 (25%)
Systemic Steroids	
Crohn's Disease	6 (7.2%)
Ulcerative Colitis	7 (8.4%)
Immunobiologic Therapy	
Crohn's Disease	12 (14.4%)
Ulcerative Colitis	4 (4.8%)

¹ percentage related to the amount of patients studied.

² percentage related to the amount of patients in clinical activity

The high prevalence of CD in the general population of Brazil has been demonstrated in several studies. Gandolfi *et al.*^[17] found a prevalence of 1: 681 in the population of blood donors of Brasilia. Although high, revealing that CD is not a rare disease in Brazil, the prevalence found in the study could be underestimated because the serological test used as initial screening was the antigliadin IgG antibody (AGA-IgG). AGA alone is a poorly sensitive test^[20-22] and IgG-based serological tests are even less sensitive in patients without selective IgA deficiency^[23]. Subsequent studies in São Paulo^[18] and Ribeirão Preto^[19], performed with a more sensitive serological screening found an even higher prevalence of 1: 214 and 1: 273, respectively, demonstrated that CD is a common disease even in the Brazilian ethnic mixed population.

The occurrence of IBD, on the other hand, is infrequent. A Brazilian study by Victoria *et al.*^[24] found IBD incidence of 22.61 cases / 100,000 inhabitants (4.48 cases / 100,000 inhabitants for UC and 3.50 cases / 100,000 inhabitants for CrD) in the period from 1986 to 2005. These results are lower than those reported in Europe and the United States^[25], and may be justified by the small population studied. However, the observation of the higher incidence and prevalence over the years shows the trend, already documented in developed countries, of the increase in the number of cases with the population socioeconomic improvement.

The choice of a sensitive serologic marker is of great importance in the initial screening of CD in a given population. Anti-endomysial and anti-transglutaminase antibodies have high sensitivity and specificity, around 95% and 100% respectively, making the dosage of anti-gliadin antibodies an obsolete test, especially in the adult population due to its low accuracy^[21]. Although some authors recommend combining serological tests in order to reduce the likelihood of false-negative results^[26], a meta-analysis conducted by Hill^[22] has shown there are no advantages in combining tests on high-sensitivity test isolated.

In the present study, anti-endomysial IgA antibody (AAE) was chosen due to its high sensitivity and specificity, comparable to anti-tissue transglutaminase antibody (TGA), and higher than that of anti-gliadin^[21,22] and because it is a strong predictor of CD regardless of initial titration^[27]. Although AAE dosage is measured by immunofluorescence, making the test dependent on the reader's experience, it has some advantages over TGA in the evaluation of patients with IBD. Tissue transglutaminase is an intracellular enzyme present in endothelial cells, smooth muscle and mesangial cells that participate in the formation of the protein matrix, catalyzing covalent reactions between amino acid residues. It can be released to the extracellular environment during episodes of infection, inflammation, mechanical stress and apoptosis, being actively involved in wound healing^[28-30]. TGA has already been identified in patients with IBD without evidence of CD, and its positivity can be attributed to tissue damage and chronic inflammatory state, suggesting low specificity of the test in this group of patients. The performance of upper gastrointestinal endoscopy with duodenal biopsy routinely in patients with IBD, in turn, is not justified as macroscopic and microscopic alterations found may generate diagnostic confusion^[31].

Regarding the possible interactions between CD and IBD, a similar pathophysiological mechanism is considered. Epidemiological studies have suggested that celiac patients and their families are more likely to develop CrD and UC than the general population^[32-34]. Cottone *et al.*^[5] evaluated 600 first-degree relatives of 111 celiac patients and found ten cases of IBD (7 cases of UC and 3 cases of CrD) compared to only one case of UC among the 1,196 first-degree relatives of the control group. Only the UC frequency was statistically significant,

suggesting an increase in the family prevalence of UC among celiac patients. Shah *et al.*^[6] identified six first-degree relatives of celiac patients diagnosed with IBD, five UC and one CrD, configuring a five-fold increased risk of IUC in relatives of celiac patients compared to the general population. Yang *et al.*^[33], in turn, studying patients with CD, diagnosed ten cases of IBD (5 with CrD and 5 with UC) and 17 cases of microscopic colitis in a population of 455 celiac patients. In this study, the prevalence ratios of UC and CrD were 3.56 and 8.49, respectively, demonstrating an increase in the prevalence of IBD in celiac patients compared to the general population. Masachs *et al.*^[32] analyzed 86 patients with CD and their first-degree relatives and found three cases of CrD and four among their relatives, against only one case in the control group of 809 individuals.

Tursi *et al.*^[11] in a small series of cases with 27 patients with CrD in Italy found a high prevalence of CD, with five patients showing serologic and histopathological duodenal mucosa compatible with CD. Tavakkoli *et al.*^[35] in a recent study in Iran found 17 patients with positive serology for TGA, 22 for AAE and nine patients with positive combined serology (AAE + TGA), six with UC and three with CrD, of 100 IBD patients evaluated. This study had as limitation the lack of histopathological confirmation of CD due to the refusal of patients to undergo high endoscopy.

Other authors, however, present important series with different results. Casella *et al.*^[14], also in Italy, evaluated 1171 patients with IBD and found CD-compatible serology and histopathology in nine (0.5%), six of which had UC and three CrD, demonstrating a low prevalence of CD among patients with IBD. Mantzaris *et al.*^[12] diagnosed CD in only one patient (0.36%) of the 281 patients with CrD, but they observed that five of the 358 patients with recent diagnosis of UC (1.4%) had concomitant CD. Leeds *et al.*^[13], in a broad study to determine the presence of CD in IBD and vice versa, evaluated 354 IBD patients and found only three (0.85%) with CD-compatible serology and histology, two with UC and one with CrD. In contrast, of the 305 celiac patients, ten were diagnosed as having IBD (five UC and five lymphocytic colitis). They concluded, therefore, that although in celiac patients the prevalence of IBD is increased by about tenfold, the prevalence of CD in patients with IBD did not differ from the control group.

The microenvironment of the gastrointestinal tract is a complex ecosystem in which there is a balance between antigenic stimuli and immune response. CD and IBD share, at first glance, several similarities in the immunopathogenesis that generates tissue damage in the intestinal mucosa. In both, there is participation of innate immunity represented by macrophages and neutrophils and adaptive immunity, consisting of T and B lymphocytes^[1,28,36]. Changes in mucosal permeability determine the exposure of luminal antigens (i.e. gluten in the case of CD and antigens of the bacterial microbiota in the case of IBD) to intraepithelial T lymphocytes present in the submucosa. These activated clones, in turn, express an abnormal and exacerbated response, characteristically of Th1 type, with decreased apoptosis and recruitment of effector cells (i.e., macrophages and neutrophils) in the intestinal interstitium, culminating in tissue damage^[1,28,30,36,37]. The maintenance of antigenic exposure and immune hyper-reactivity contribute to the continuous intestinal inflammation typical of these conditions.

Some authors believe that the higher prevalence of CD in patients with IBD and vice versa may be justified by these immunocellular similarities^[11,30,32]. However, Savilahti *et al.*^[40] observed that the population of intraepithelial lymphocytes involved in CD and IBD are different. While in CrD and UC, there is a predominance of lymphocytes with α / β type cell receptor, similar to the intestine

of normal individuals, in CD, there was a marked increase in the lymphocyte population with γ / δ cell type receptor, now considered the CD marker, serving as the connection between innate and adaptive immunity^[28].

Alteration of mucosal permeability is a crucial event in the pathogenesis of both CD and IBD, whereby, as described above, luminal antigens are exposed to immune cells. Some authors suggest that breaking the integrity of the intestinal mucosal barrier that accompanies IBD would allow exposure to the immune system of various bacterial products that would mimic the 57-68 and / or 62-75 sequences of the gliadin and, through immunological activation via Th1 response, would trigger CD lesions^[11,30]. This hypothesis could also justify the higher occurrence of IBD in celiac patients, since the increase in the mucosal permeability generated by CD would cause greater translocation of bacterial antigens, an event implicated in the pathogenic mechanism of IBD^[35]. The demonstration of high prevalence of seropositivity for anti-Saccharomyces cerevisiae (ASCA) antibody, as a serological marker for CrD in celiac patients^[30,38] may reinforce these assumptions.

Genetically, no common susceptibility was found between CD and CrD. There does not seem to be any relationship between the latter and genes components of the HLA system. Thus, only individuals with CrD harboring DQ2 or DQ8 alleles would be at risk of developing CD. Glas *et al*^[39], on the other hand, demonstrated that the polymorphism on 4q27 chromosome, region of interleukins 2 and 21 (IL-2 and IL-21) associated with CD are also found in cases of UC but not of CrD. This and other recent studies have suggested a common genetic component between CD and UC.

The present study, in agreement with other publications^[12-14], opposes the theory that patients with inflammatory bowel diseases would have higher prevalence of associated celiac disease^[11,35]. The main limitation of this study is that the study population is considered low compared to previous publications^[12-14]. However, the prevalence of CD in Brazil is not considered low^[18], even though Brazil has an essentially ethnic mixed population. Thus, the results obtained are important to demonstrate that there is no need to routinely investigate the presence of CD in patients with any form of IBD, since higher prevalence of CD in this subgroup of patients has not been demonstrated.

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