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The association between *de novo* inflammatory bowel disease and celiac disease

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CONFLICTS OF INTEREST

Noemí Manceñido Marcos has been a speaker for Janssen, Takeda, Shire and Abbvie. The other authors have no conflicts of interest to report.

ABSTRACT

Introduction: controversial data have been reported on the potential association between celiac disease (CeD) and inflammatory bowel disease (IBD).

Objective: to study the prevalence of CeD in patients newly diagnosed cases with IBD.

Methods: an observational, retrospective study was performed in patients with newly diagnosed IBD who were screened for CeD by anti-tissue transglutaminase antibodies (anti-tTG) measurements and an endoscopic duodenal biopsy. No patients had received corticosteroids, immunosuppressants or biologic drugs within the three months prior to gastroscopy. In the presence of Marsh 1, other causes were ruled out. CeD was diagnosed in patients positive for anti-tTG, compatible duodenal biopsy findings and a good response to a gluten-free diet.

Results: a total of 163 patients were screened for CeD. Of these, six (3.7%) were positive for anti-tTG and four were diagnosed with CeD (three had ulcerative colitis, one had Crohn's disease). All

patients with both CeD and IBD had normal IgA levels, positive anti-tTG and CeD genetic markers.

Conclusions: the prevalence of CeD in our patients with IBD was higher than that reported in the literature for other series of patients with IBD. A combination of anti-tTG testing and CeD genetics may screen patients for CeD in this population of patients with IBD.

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

INTRODUCTION

Celiac disease (CeD) is an immune-based chronic enteropathy that occurs in genetically predisposed individuals (human leukocyte antigen [HLA] DQ2 and DQ8). The condition is induced by dietary gluten and likely, by other environmental factors. The disease exhibits a wide-ranging clinical heterogeneity with a significant morbidity and mortality. It is estimated that celiac disease may affect around 1% of the Western general population and 15-20% of first-degree relatives of celiac patients (1).

Inflammatory bowel disease (IBD) represents a set of clinical conditions characterized by chronic inflammation, a waxing and waning course of an unknown origin and primary gut involvement. IBD includes Crohn's disease (CD) and ulcerative colitis (UC); the clinical and pathological characteristics of these entities may occasionally overlap. There is also a third variant called indeterminate or unclassified colitis (IC), where neither of the two former diagnoses can be made (2,3). The incidence and prevalence of these diseases have been on the rise of late, particularly for CD but also for UC.

Multiple reports describe an association between CeD and IBD, mostly based on isolated case reports or smaller series of patients (4-9). The timing of CeD and IBD diagnosis is variable. Sometimes CeD is diagnosed before IBD (8) and other times IBD is diagnosed before CeD (7) and occasionally, IBD and CeD are diagnosed at the same time (5,6).

The prevalence of IBD in CeD patients has been reported to be up to 5-10 times higher than in the general population (4). Furthermore, a higher prevalence of CeD has been reported in patients with IBD, particularly CD (9,10). In addition, when both conditions concur, their prognoses and outcomes seem to be worse, with an increase in the morbidity and mortality associated with both diseases. Patients with CeD and UC more commonly have pancolitis or extensive colitis, use more immunomodulators (10,11) and undergo more colectomies due to a more aggressive UC (4,11).

Patients with CeD and IBD have higher mortality rates from colon cancer and non-Hodgkin lymphoma (12) and an increased association with primary sclerosing cholangitis (11). However, this association is controversial as some studies have not found a significant association between both conditions (13).

While the possible origin of this association remains unknown, CeD and IBD have been posited to potentially share the same HLA class II haplotype or other susceptibility loci (14-16). Furthermore, an antigen activates several inflammatory cascades in both conditions. This results in damage to the intestinal mucosa (16), which results in increased permeability at intercellular junctions. This in turn augments antigen (dietary or otherwise) presentation and bacterial translocation, factors that have also been implicated in the pathogenesis of IBD, especially of CD (17,18).

CeD is difficult to diagnose on occasion, even more so in patients with IBD. It has been reported that patients with IBD have high levels of anti-tissue transglutaminase antibodies (anti-tTG) (19,20), with a potential correlation between anti-tTG titers and disease activity. This may result in higher rates of false positives in patients with IBD (20). In addition, clinical manifestations and histology findings may be similar particularly in the case of CD. Furthermore, CeD should be ruled out in patients with CD (2), particularly in those with refractory IBD (11).

Given the controversial, though potential association between CeD and IBD and the small number of studies performed thus far in Spain, this study aimed to determine the prevalence of CeD in newly diagnosed IBD patients in our hospital area.

MATERIAL AND METHODS

An observational, retrospective study was performed in a single center that served a population of over 303,000 inhabitants in the northern area of the Autonomous Community of Madrid (Spain). Newly diagnosed IBD patients were enrolled into the study between February 2008 and May 2012. The Lennard-Jones criteria were used for the diagnosis of IBD (21) and the Montreal classification was used to define UC location and CD characteristics (2,3). Patients with a prior diagnosis of CeD were excluded. Data for analysis were obtained from a review of the electronic medical records (Selene®, Cerner).

IgA and anti-tTG-IgA levels were measured in patients *de novo* diagnosed with IBD. IgA, IgG and anti-tTG-IgG levels were measured in patients with IgA deficiency using highly sensitive techniques. Anti-tTG levels were measured again after 3-6 months in patients with indeterminate

levels. Immunoturbodimetry was used to measure IgA and IgG levels. High-sensitivity IgA levels were measured via nephelometry and both anti-tTG types (IgA and IgG) were tested using an ELISA. No patient was under treatment with immunosuppressants, biologics or cortiscosteroids at the time of anti-tTG testing.

A genetic study of CeD susceptibility was performed in patients with a history of CeD, positive anti-tTG or a high diagnostic suspicion of CeD in the presence of negative anti-tTG. HLA heterodimers DQ2/DQ8 were assessed using polymerase chain reaction (PCR) methods. HLA-Class II alleles DQA1*, DQB1* and DRB1* were also assessed, which allowed us to establish the presence of celiac disease-associated haplotypes DR3-DQ2, DR7-DQ2, DR5-DQ7 and DR4-DQ8.

Patients positive for anti-tTG underwent an upper digestive endoscopy with multiple biopsy samples taken from the proximal small bowel (duodenal bulb and/or second portion). No patients had previously received treatment with corticosteroids, immunosuppressants or biologics within the three months prior to the procedure. All patients undergoing upper GI endoscopy signed an informed consent form for the procedure.

Sample processing at the Pathology Department was performed following the standard protocol. The Marsh-Oberhuber classification was used for the histological diagnosis of CeD (22). In cases where a duodenal biopsy revealed intraepithelial lymphocytosis (Marsh 1), the presence of gastric infection with *Helicobacter pylori* (HP) was assessed by gastric biopsy (with histological and immunohistochemical staining or a rapid urease test) or a HP breath test according to standard protocols. The use of nonsteroidal anti-inflammatory drugs and the presence of fecal parasites were also ruled out. Additional potential causes were also excluded when there was a diagnostic uncertainty of the origin of intraepithelial lymphocytosis after performing all the tests.

Data were analyzed using the SPSS v.21.0 statistical software. Qualitative variables are described as absolute or relative frequencies (n) and percentages (%) for each category. Qualitative variables were analyzed using contingency tables, Pearson's Chi-squared test and Fisher's test for small sample sets. Odds ratios (OR) and 95% confidence intervals (CI) were calculated whenever possible. Quantitative variables were expressed as the mean and standard deviation and were analyzed using the Student's t-test or Mann-Whitney U test as needed. Statistical significance was set at $p < 0.05$.

RESULTS

During the above-mentioned period, 163 newly diagnosed IBD cases (65 with CD, 92 with UC, six with IC) were screened for CeD. The mean age at diagnosis with IBD was 37.58 ± 14.58 years, with a range of 14 to 75 years, and 46.63% were male. Table 1 shows the characteristics of the IBD patients included in the study. Of these, only three cases (1.84%) had decreased IgA levels, they were all CD cases (4.61% of patients with CD) and no statistically significant differences were found (p = 1.44 when comparing CD *vs* UC *vs* IC).

Six patients were positive for anti-tTG (3.68% of patients) and all patients positive for anti-tTG had normal IgA levels. The mean age at diagnosis with IBD was 33.33 years for patients positive for anti-tTG and 37.74 years for those negative for anti-tTG (p = 0.540). Of the six patients positive for anti-tTG, five were female. With regard to race, five were white and one was Hispanic and none had a family history of CeD. Regarding IBD type, two patients positive for anti-tTG had CD, four had UC and no statistically significant differences were found (CD *vs* UC *vs* IC, p = 0.730; CD *vs* UC, p = 0.999).

CeD-related HLA was screened in 13 patients, seven with CD and six with UC. CeD-related HLA was positive in five patients with CD and three with UC, with no statistically significant differences between the groups (p = 0.635). A genetic study was performed for all patients that were positive for anti-tTG (n = 6) and some negative for anti-tTG. Of the eight patients with CeD-related HLA, five were female and five were white, two Hispanic and one Arab. IgA levels were normal in six of eight patients with positive CeD-related HLA, IgA levels were decreased in one case and unknown in another case. Of patients positive for anti-tTG, five had positive CeD-related HLA and two of these had CD and three had UC.

Six patients positive for anti-tTG underwent a duodenal biopsy; four had UC (two ulcerative proctitis, two extensive colitis) and two had CD (one colonic CD, one ileocolonic CD). None of these patients was using or had previously used immunosuppressants, biologics or oral steroids at the time of their duodenal biopsy. The duodenal biopsy was normal in two of these six patients and there were histologic changes consistent with CeD in four. Among the latter, three had UC (two ulcerative proctitis, one extensive colitis) and one had ileocolonic CD. Other causes were ruled out and response to gluten-free diet was tested in two cases with Marsh 1 histology. According to these data, four (2.45%) of 163 patients screened for CeD had serological and histological evidence of CeD. The clinical characteristics of CeD patients are shown in table 2 and table 3 shows the clinical characteristics of patients positive for anti-tTG with a normal duodenal biopsy.

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DISCUSSION

This study set out to assess the prevalence of CeD in newly diagnosed IBD cases, without interference from treatments or situations that might potentially hinder a diagnosis. This is important as CeD should be diagnosed concurrently, with or immediately after IBD. Furthermore, no patients were under treatment with corticosteroids, biologics or immunosuppressants at the time of anti-tTG testing or biopsy. No recent reports were found in the literature that assessed this association in adult patients in Spain, which enhances the relevance of our study.

Only six (3.7%) of 163 patients were positive for anti-tTG. Although serum tests for CeD are highly specific (23,24), the presence of anti-tTG in IBD has been reported without implying a diagnosis with CeD. Hence, some authors recommend that CeD be screened in this population with anti-tTG and anti-endomysium antibodies (EMA) in association with HLA testing and a duodenal biopsy (19,25,26). However, in this series, only two of six patients positive for anti-tTG were found to be false-positive cases. Anti-tTG rates in the study population are clearly lower than that reported in other studies: 27.3% of patients with CD in a Spanish study (27) and 18.5% of patients with CD in an Italian research (9) were positive for anti-tTG.

Remarkably, all six patients that were positive for anti-tTG had colonic involvement, regardless of IBD type (two ulcerative proctitis, two extensive colitis, one ileocolonic CD, and one colonic CD). No conclusive evidence exists in the literature about whether anti-tTG testing in IBD patients may be influenced by disease activity or location (19,28). Both false-positive anti-tTG and positive anti-tTG tests related to IBD might explain our case with UC, a positive anti-tTG, negative genetics and a normal duodenal biopsy. In the patient with ileocolonic CD, positive anti-tTG and genetics tests and a normal duodenal biopsy, anti-tTG might be a false positive or in fact positive as a result of IBD activity. Thus, the latent or potential CeD might not be ruled out. In this case, the patient is being monitored for potential CeD, as recommended in the literature (24). However, false positive anti-tTG results in patients with IBD do not seem to be an issue for the diagnosis of CeD, since most centers have CeD-related HLA testing available. A negative CeD-related HLA result would rule out CeD with a negative predictive value > 99% and a positive result would prompt an upper endoscopy with a duodenal biopsy to confirm a CeD diagnosis (1,24). Therefore, combining anti-tTG and CeD genetic testing in patients with IBD allows the screening of CeD in these patients, as well as in the general population.

This study is relevant since no real-world studies exist on the prevalence of CeD in adult patients with IBD among the Spanish population. The prevalence of CeD in patients with IBD was 2.45% in our study, which is clearly higher than that reported in other series of patients with IBD. The prevalence of CeD in the United Kingdom was 0.8% (4/354 patients, two with UC and two with CD) (29) and 0.5% in Italy, with a higher rate for UC (13,20). This might be accounted for by the presence of unidentified genetic, ethnic or environmental factors. While the low number of patients precludes other analyses, CeD does seem to be associated with colonic IBD in the study population.

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Table 1. Characteristics of study patients with IBD

	Total	*CD*	*UC*	*IC*
Age (years) (mean ± standard deviation)	37.58 ± 14.58	33.58 ± 13.41	39.79 ± 14.53	46.83 ± 18.58
Gender (n [%])				
Males	76 (46.63)	37 (56.92)	35 (38.04)	4 (66.7)
Race (n [%])				
White	153 (93.87)	59 (90.77)	88 (95.65)	6 (100)
Hispanic	4 (2.45)	2 (3.08)	2 (2.17)	0 (0)
Arab	6 (3.68)	4 (6.15)	2 (2.17)	0 (0)
Tobacco (n [%])				
Smokers	34 (20.86)	19 (29.23)	13 (14.13)	2 (33.33)
Ex-smokers	25 (15.34)	10 (15.38)	13 (14.13)	2 (33.33)
Family history with CeD	1 (0.61)	1 (1.54)	0	0
Reduced IgA	3 (1.84)	3 (4.62)	0	0
Positive anti-tTG	6 (3.68)	2 (3.08)	4 (4.35)	0

Table 2. Clinical characteristics of patients with celiac disease

	Case 1	*Case 2*	*Case 3*	*Case 4*
Gender	Male	Female	Female	Female
Race	Caucasian	Caucasian	Caucasian	Caucasian
Age at diagnosis	34	40	32	26
IBD type*	Crohn's disease L2B1A2	Ulcerative colitis E1	Ulcerative colitis E1	Ulcerative colitis E3
IgA	Normal	Normal	Normal	Normal
anti-tTG	Positive	Positive	Positive	Positive
HLA	Positive	Positive	Positive	Positive
HLA type	HLA DQ8 (DR4-DQ8)	HLA DQ2 (DR7-DQ2)	HLA DQ8 (DR4-DQ8)	HLA DQ2 (DR7-DQ2)
Duodenal histology†	Marsh 3b	Marsh 3c	Marsh 1	Marsh 1

*According to the Montreal classification. †According to the Marsh-Oberhuber classification.

Table 3. Clinical characteristics of patients positive for anti-tTG with a normal duodenal biopsy

	Case 1	*Case 2*
Gender	Female	Female
Race	Hispanic	Caucasian
Age at diagnosis	53	15
IBD type*	Ulcerative colitis E3	Crohn's disease L3B1A1
IgA	Normal	Normal
anti-tTG	Positive	Positive
HLA	Negative	Positive
HLA type	-	HLA DQ2 (DR7-DQ2/ DR5-DQ7)
Duodenal histology†	Normal	Normal

*According to the Montreal classification. †According to the Marsh-Oberhuber classification.