Inflammatory Bowel Disease in Patients with Celiac Disease

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Background: Several case reports and series report an association between celiac disease and inflammatory bowel disease (IBD); however, there is no current data assessing this association. We therefore studied the occurrence of these conditions in a cohort of patients with celiac disease seen at a referral center.

Methods: A database of patients with celiac disease seen between 1981 and 2002 was analyzed. Only biopsy-proven adults were included. Patients who had endoscopic and pathologic evidence of IBD were identified, and their pathology was reviewed. Age- and sex-adjusted prevalence rate ratios were determined by comparing results with population-based prevalence data.

Results: Among 455 patients with celiac disease, IBD was identified in 10 (5 had ulcerative colitis and 5 had Crohn's disease). This represented an age- and sex-adjusted prevalence rate ratio for ulcerative colitis of 3.56 (95% confidence interval, 1.48–8.56) and for Crohn's disease of 8.49 (95% confidence interval, 3.53–20.42).

Conclusion: Within our cohort of patients with celiac disease, IBD was significantly more common than in the general population.

Key Words: celiac disease, inflammatory bowel disease

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Celiac disease is a genetically determined chronic inflammatory disease of the small intestine. Serologic screening studies suggest that it occurs in about 1% of the population worldwide.[1,2] The clinical prevalence does not approach this prevalence, although the rate of diagnosis of celiac disease is increasing in the United States.[3]

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Celiac disease is associated with autoimmune disorders[4,5] that frequently present before diagnosis of celiac disease.[6,7] Often the associated autoimmune disease is more clinically significant than celiac disease, although there is evidence that celiac disease may be the initial problem that allows the associated autoimmune disease to develop.[5,8]

Several case reports and case series have suggested an association between celiac disease and inflammatory bowel disease (IBD),[9–14] most frequently ulcerative colitis (UC).[15–20] There has, however, been no recent literature concerning this relationship. We therefore reviewed the occurrence of IBD among a cohort of biopsy-proven patients with celiac disease.

MATERIALS AND METHODS

An anonomized database of patients with celiac disease seen at the Columbia University Medical Center between 1981 and 2002[21] was reviewed. Biopsy-proven patients who fulfilled eligibility criteria of age greater than 18 years, together with clinical or histologic response to a gluten-free diet, were identified. Among those patients, we identified those in whom there was also a diagnosis of IBD. The patients with IBD were included if clinical history was supported by endoscopic and pathologic confirmation of diagnosis. The pathology was reviewed to confirm the diagnoses. The age- and sex-adjusted prevalence rate ratio was calculated with Poisson regression models by comparing the prevalence of IBD in our cohort to the prevalence of IBD in the U.S. population.[22,23] Analysis was conducted using Statistical Analysis Software (SAS 8.2, SAS Institute Inc., Cary, N.C.).

RESULTS

Patient Populations

The cohort consisted of 455 patients, with a mean age of 44.8 ± 17.6 (SD) years. There were 303 women and 152 men. IBD was diagnosed in 10 patients (2.2%; 5 had UC and 5 had Crohn's disease [CD]). Microscopic colitis was twice as common, occurring in 17 patients (3.7%).

Patients with CD

CD was present in 5 patients (3 women and 2 men); the distribution of CD was the colon in 3 and ileo-colitis in 2 of the

patients (Table 1). The initial diagnosis in these patients was CD in 2 and celiac disease in 3. Two patients had a childhood diagnosis of celiac disease. They were considered to have grown out of the disease and were rediagnosed with celiac disease as adults. The second diagnosis, either celiac disease or CD, occurred 1 to 12 years after the diagnosis as an adult. No patient had evidence of CD in the duodenum to account for the villous atrophy. In addition, each patient had serologic evidence of celiac disease (endomysial antibody or tissue transglutaminase antibodies) or an unequivocal response to a gluten-free diet. One patient had selective IgA deficiency. Two patients had features of lymphocytic colitis as well as CD, identified in colonic biopsies.

Patients with UC

Among the 5 patients with UC, 4 were women and 1 was a man (Table 2). Three of the patients underwent total colectomy because of refractory disease. Celiac disease was diagnosed in the same month as the colitis in 1 patient and 5 and 3 years after colectomy in 2 patients: 1 because of persistent diarrhea and the other because of the presence of iron deficiency anemia. Another patient presented with rectal bleeding, caused by ulcerative proctitis, 4 years after the diagnosis of celiac disease was established by screening (celiac disease was diagnosed in her daughter). The man presented with erythema nodosum and rectal bleeding 20 months after the diagnosis of celiac disease.

To determine if the prevalence of IBD was increased in this cohort of patients with celiac disease compared with the general population, we determined the age- and sex-adjusted prevalence rate ratio of both UC and CD using population-based data from the United States. For UC, this value was 3.56 (95% confidence interval [CI], 1.48–8.56) and for CD, the value was 8.49 (95% CI, 3.53–20.42), both of which were significantly increased.

DISCUSSION

In our cohort of patients with celiac disease, the age- and sex-adjusted prevalence rate ratio of UC and CD was 3.56 (95% CI, 1.48–8.56) and 8.49 (95% CI, 3.53–20.42), respectively, showing an increased prevalence of IBD in patients with celiac disease compared with the general population. All the patients in this cohort were attending a University-based celiac disease center, introducing a referral bias for more unusual or complicated patients with celiac disease. Another contributing factor to the increased prevalence of IBD in our cohort of patients with celiac disease from New York is the large number with Jewish ancestry,[24] a group in whom IBD is more common than in other ethnic groups.[25,26]

There is already a considerable body of literature supporting an association between celiac disease and IBD. In 1965, Salem and Truelove[27] showed that 20% of patients with UC had villous atrophy in duodenal biopsies. Studies from the United Kingdom,[7,11,16] Sweden,[12] and the United States[28] have reported an increased prevalence of UC[7] and CD[28] in patients with celiac disease. These studies had shown a 2- to 10-fold increase in the incidence of patients with both IBD and celiac disease than would be expected by chance.[11,12,16]

In addition, multiple cases series and single case reports have reported an association of celiac disease with

TABLE 1. Patients with CD and Celiac Disease

Sex/Age (yr)	Initial Diagnosis and Course	Time to Second Diagnosis	Second Diagnosis and Clinical Course
Male/76	Crohn's colitis Responded to ASA	10 years	Celiac disease (diarrhea) EMA+, PVA, responded to GFD
Male/69	Crohn's ileocolitis, ASCA+ Responded to ASA, steroids, Infliximab	2 years	Celiac disease (diarrhea) tTG+, PVA, improved on GFD
Female/57	Celiac disease (diarrhea) EMA+, TVA, Responded to GFD	1 years	Crohn's disease (bleeding and diarrhea), responded to ASA and prednisone
Female/63	Celiac disease diagnosed in childhood, rediagnosed at age 53, diarrhea, IgA deficient, IgG AGA+, PVA, improvement on GFD	4 years	Crohn's disease (bleeding) Left-sidedcolitis, responded to ASA
Female/57	Celiac disease diagnosed in childhood, rediagnosed at age 43, diarrhea, EMA+, TVA, resolution on GFD	12 years	Crohn's colitis (abdominal pain and bleeding), responded to ASA

PVA, partial villous atrophy; TVA, total villous atrophy; EMA+, positive endomysial antibody; tTG+, positive tissue transglutaminase antibody; ASCA, anti-*Saccharomyces cerevisiae* antibody; ASA, 5-ASA–containing drug; GFD, gluten-free diet; IgG, AGA+ positive anti-IgG antigliadin antibody.

TABLE 2. Patients with UC

Sex/Age (yr)	Initial Diagnosis and Course	Time to Second Diagnosis	Second Diagnosis and Clinical Course
Female/68	UC, pancolitis, refractory to therapy, proctocolectomy at age 60	46 years	Celiac disease, (iron deficiency anemia, EMA+, TVA, response to GFD
Female/39	UC, pancolitis, refractory to therapy, proctocolectomy at age 34	8 years	Celiac disease, (nausea, diarrhea), EMA+, TVA, improved on GFD
Female/46	Celiac disease, EMA+ on screening because of family history, PVA	4 years	UC, proctitis , (bleeding) Responded to ASA
Male/31	Celiac disease, (diarrhea), tTG+, TVA, improved on GFD	7 months	UC (erythema nodosum, bleeding), pancolitis, responded to ASA, steroids
Female/43	Celiac disease, (bloating and diarrhea), tTG+, PVA. Normalization after 2 years on GFD.	Same month	UC, bleeding, pancolitis, no response to steroids, cyclosporine, proctocolectomy

PVA, partial villous atrophy; TVA, total villous atrophy; EMA+, positive endomysial antibody; tTG+, positive tissue transglutaminase antibody; ASCA, anti-*Saccharomyces cerevisiae* antibody; ASA, 5-ASA–containing drug; GFD, gluten-free diet; IgG, AGA+ positive anti-IgG antigliadin antibody.

IBD.[10,12,14,16,19,29,30] Most of the case series have shown an association with celiac disease and UC,[15,16,18,30] with an associated sclerosing cholangitis in some patients.[20,31] However both CD[13,32] and ulcerative proctitis have been reported in association with celiac disease.[15] The increased association of the diseases also extends to first degree relatives.[9,17] In 1 study, the relative risk of UC was 5 times greater for first degree relatives of patients with celiac disease than for the general population (5.0; 95% CI, 4.7–7.2).[9]

In addition, support for an association between celiac disease and IBD comes from a recent large population-based study of mortality in Swedish patients with celiac disease. In this study, standardized mortality ratios were determined for a large number of patients with celiac disease hospitalized between 1964 and 1993; the mortality risk for a variety of diseases was increased. The standarized mortality ratio for IBD was 70.9 (95% CI, 36.6–123.9). This 70-fold excess mortality compares with a 17.3-fold excess risk of dying from small intestinal cancer and 11.4-fold excess risk of dying from non–Hodgkin's lymphoma, both well-accepted complications of celiac disease.[33,34] This increased risk for IBD was based on 12 patients, of whom 6 died from UC and 6 from CD.[35] In a study describing the mortality rate in a series of patients with celiac disease from Denmark, 2 patients died of complications of colitis.[36] These studies suggest that not only is there an association between IBD and celiac disease, but when occurring together, there is a worse outlook. In our series, 3 patients with UC required colectomy as the ultimate therapy for UC, indicative of the severity of the UC.

The patients in our study had unequivocal biopsy findings with histologic, serologic, or clinical improvement on a gluten-free diet consistent with celiac disease, in addition to endoscopic and pathologic evidence of IBD. However, celiac disease and IBD (CD and UC) are both chronic inflammatory conditions of the intestines, and there is a possibility of confusion, pathologically, between them. This is unlikely for UC and celiac disease. However, because CD may involve the upper small intestine, there is potential for misdiagnosis. In 1 well-documented case, all grades of villous atrophy were reported in small intestinal biopsies of a patient with CD.[37] In addition, Wright and Riddell,[38] in a retrospective review of upper gastrointestinal pathologic findings in patients with CD, found villous atrophy in 23% of patients and intraepithelial lymphocytosis in 22%. This surprising finding had not previously been reported or confirmed in other studies. These are usually findings of celiac disease; however, the investigators did not raise the possibility of celiac disease, despite these findings. Pathologists need to be aware that both conditions can coexist in any given patient.

Serologic tests should assist in the differentiation between celiac disease and CD. Most patients with celiac disease have positive endomysial or tissue transglutaminase antibodies. Endomysial antibodies are specific for celiac disease[39] and are not found in CD.[40] Tissue transglutaminase IgA antibodies have, however, been reported to be present in patients with both UC and CD.[40] A diagnosis of celiac disease is more difficult to entertain when serologic tests (antiendomysial and tissue transglutaminase antibodies) are negative.

However, negative serologies do occur in patients with celiac disease, especially in the presence of lesser degrees of villous atrophy.[41–43] Anti–*Saccharomyces cerevisiae* antibodies are usually indicative of CD but may be seen in patients with celiac disease.[44]

An increase in the diagnosis of both celiac disease and IBD may also reflect an increase in the use of endoscopy (both colonoscopy and esophagogastroduodenoscopy), with subsequent diagnosis of conditions that would otherwise remain undetected.[35] Similarly, more widespread use of serologic testing and endoscopic assessment may allow the diagnosis of celiac disease or IBD in patients that may have received alternate diagnoses such as an irritable bowel syndrome.[45] Our results must also be interpreted in the setting of an increase in the incidence of both IBD[22,46–48] and celiac disease.[3]

Our study confirms earlier studies showing an association of celiac disease and IBD. For our cohort, the risk was greater for those with CD than UC. The prevalence of celiac disease in patients with IBD and its impact on the course of the patient's illness need to be assessed.

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