The Prevalence of Celiac Disease Among Patients With Nonconstipated Irritable Bowel Syndrome Is Similar to Controls

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BACKGROUND & AIMS: Guidelines recommend that patients with symptoms of nonconstipated irritable bowel syndrome (NC-IBS) undergo testing for celiac disease (CD). We evaluated the prevalence of CD antibodies, and biopsy confirmed CD among patients with NC-IBS in a large US population. **METHODS:** In a study conducted at 4 sites, from 2003 to 2008, we compared data from 492 patients with symptoms of NC-IBS to 458 asymptomatic individuals who underwent colonoscopy examinations for cancer screening or polyp surveillance (controls). All participants provided blood samples for specific and nonspecific CD-associated antibodies. Additionally, patients with IBS were analyzed for complete blood cell counts, metabolic factors, erythrocyte sedimentation rates, and levels of C-reactive protein and thyroid-stimulating hormone. Any subjects found to have CD-associated antibodies were offered esophagogastroduodenoscopy and duodenal biopsy analysis. **RESULTS:** Of patients with NC-IBS, 7.3% had abnormal results for CD-associated antibodies, compared with 4.8% of controls (adjusted odds ratio, 1.49; 95% confidence interval: 0.76–2.90; $P = .25$). Within the NC-IBS group, 6.51% had antibodies against gliadin, 1.22% against tissue transglutaminase, and 0.61% against endomysium ($P > .05$ vs controls for all antibodies tested). CD was confirmed in 0.41% of patients in the NC-IBS group and 0.44% of controls ($P > .99$). **CONCLUSIONS: Although CD-associated antibodies are relatively common, the prevalence of CD among patients with NC-IBS is similar to that among controls in a large US population. These findings challenge recommendations to routinely screen patients with NC-IBS for CD. More than 7% of patients with NC-IBS had CD-associated antibodies, suggesting that gluten sensitivity might mediate IBS symptoms; further studies are needed.**

Keywords: Population Study; Epidemiology; Celiac Disease Incidence; Inflammation.

The presence of gastrointestinal (GI) symptoms suggestive of the irritable bowel syndrome (IBS) is one of the most common reasons for referral to a gastroenterology specialist in the United States. IBS has been estimated to affect approximately 10%–20% of the American population,[1] and similar prevalence estimates have been reported from other countries.[2,3] The societal impact of IBS is significant, both in terms of direct and indirect costs as well as the impaired health-related quality of life that patients with IBS experience.[4–6]

IBS is one of a group of functional GI disorders[7] and is characterized by a lack of reproducible or reliable physical abnormalities, biomarkers, or radiologic findings. Multiple symptom-based diagnostic criteria for IBS have been developed in an attempt to simplify and standardize its diagnosis. Manning et al created the first group of diagnostic criteria in 1978.[8] The Rome Committee, a multinational consensus group of experts in functional GI disorders, created another set of criteria, ostensibly to improve the quality of clinical trials in the field of IBS.[9] Since their development, the Rome criteria for IBS have been modified several times, based on evolving evidence regarding the epidemiology, pathophysiology, and natural history of the condition.[10–13]

Celiac disease is an autoimmune GI disease that can result in symptoms similar to IBS and has an estimated prevalence of 0.7%–1% in Western populations.[14] Celiac disease has been linked to other conditions including, but not limited to, diabetes, dermatitis herpetiformis, osteoporosis, infertility, and lymphoma. Celiac disease occurs when genetically susceptible patients are exposed to dietary gluten. The vast majority of individuals with celiac disease possess human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8, and these HLA haplotypes appear to be central to the pathophysiologic basis of celiac disease via the presentation of gluten peptides to $CD4^+$ T cells in the small bowel mucosa. The presentation of these peptides can result in the activation of intraepithelial lymphocytes via amplifying mechanisms that can ultimately lead to

Abbreviations used in this paper: AGA-IgA, anti-gliadin immunoglobulin A; AGA IgG, anti-gliadin immunoglobulin G enzyme-linked immunosorbent assay; aOR, adjusted odds ratio; CD, celiac disease; CI, confidence interval; IBS, irritable bowel syndrome; IBS-D, IBS with diarrhea; IBS-M, IBS with a mixed bowel pattern; IEL, intraepithelial lymphocytes; Ig, immunoglobulin; NC-IBS, nonconstipated irritable bowel syndrome.

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damage to the intestinal epithelium in the form of villous atrophy and eventually to the development of GI symptoms, many of which can mimic IBS. Whereas much has been learned about the pathophysiology of celiac disease, much remains to be discovered, such as why some individuals with celiac disease fail to develop clinically significant symptoms despite continued gluten intake.

While celiac disease should be considered in the differential diagnosis of patients with IBS symptoms, it is not clear whether the prevalence of celiac disease among patients with IBS is high enough to warrant routine screening. A recent systematic review and a meta-analysis concluded that biopsy-proven celiac disease was 4-fold more prevalent among patients with symptoms suggestive of IBS than in persons without such symptoms.[15–16] Unfortunately, almost all of the studies included in these analyses were from outside of the United States. This is potentially important because the most recent evidence-based guidance document on the management of IBS offered by the American College of Gastroenterology (ACG) IBS Task Force recommended that patients with clinical features suggestive of IBS with diarrhea (IBS-D) or IBS with a mixed bowel pattern (IBS-M) undergo routine serological screening for celiac disease.[17]

Herein, we report the findings from the first prospective, multicenter US study comparing the prevalence of abnormal celiac antibodies and biopsy-proven celiac disease in patients with nonconstipated IBS to that of healthy volunteers undergoing routine colorectal cancer screening.

Material and Methods

This was a multicenter, prospective, observational cohort study conducted at 4 US sites between August 2003 and August 2008 (National Naval Medical Center: Bethesda, MD; Naval Medical Center: Portsmouth, VA; Walter Reed Army Medical Center: Washington, DC; and the University of Michigan: Ann Arbor, MI). There were 2 study populations enrolled in this study. An IBS group composed of consecutive patients with symptoms suggestive of nonconstipation predominant IBS (NC-IBS) who did not have alarm features suggestive of organic disease. Alarm features included symptoms such as unexplained weight loss, fever, significant GI bleeding, or historical features such as a family history of a first-degree relative with colon cancer, celiac disease, or inflammatory bowel disease (IBD). A control group consisted of asymptomatic persons undergoing colonoscopy for colorectal cancer screening or polyp surveillance. The institutional review boards at each site approved this protocol, and all patients provided informed consent prior to study participation.

Study Population

Adult patients aged 18–80 years old with symptoms suggestive of IBS were identified in the Gastroenterology clinics at the participating sites. Eligible patients with suspected NC-IBS fulfilled the Rome II criteria for IBS based on their responses to a questionnaire administered in the clinic.[18] Patients who fulfilled criteria for constipation-predominant IBS were not eligible for enrollment because of the design of the study and inclusion of diagnostic evaluations, such as colonoscopy, that were not thought to be clinically appropriate for patients with constipation-predominant IBS.

Patients in the IBS group were referred from their primary or secondary care physicians for a diagnostic evaluation of their IBS symptoms. Patients were excluded from the study if they had been previously diagnosed with comorbid conditions that could have explained their GI symptoms (eg, celiac disease, colon cancer, IBD, scleroderma, small intestinal bacterial overgrowth, uncontrolled thyroid disease, or diabetes). Patients with previous GI or intestinal (large or small bowel) surgery, with the exception of appendectomy or cholecystectomy, were also excluded. Patients reporting alarm features were not eligible for enrollment, nor were women who were pregnant or breastfeeding, or patients who had undergone previous diagnostic testing for their IBS symptoms. No participants had been previously tested for celiac disease.

The control group consisted of individuals who were scheduled for screening or surveillance colonoscopy, either because of primary care referrals or self-referral. Controls were recruited from the procedure units of the participating study sites prior to their colonoscopy. All controls completed the same Rome II GI symptom questionnaire to confirm the absence of IBS symptoms. Patients with IBS symptoms, a history of colorectal cancer, or other organic GI disease were not eligible to serve as controls.

Experimental Protocol

Participants provided blood samples for celiac disease antibody panels and HLA typing prior to undergoing colonoscopy. The celiac disease antibody panels included the following tests: anti-gliadin immunoglobulin (Ig) G enzyme-linked immunosorbent assay (AGA IgG) with a reference range <10 U/mL, anti-gliadin IgA (AGA-IgA) with a reference range <5 U/mL, anti-human tissue transglutaminase IgA enzyme-linked immunosorbent assay with a reference range <4 U/mL, anti-endomysial IgA indirect immunofluorescence assay using monkey esophagus as the substrate, and total serum IgA by nephelometry with a reference range of 44–441 mg/dL. HLA-DQ2 and HLA-DQ8 were determined using polymerase chain reaction amplification and 72 probe hybridizations for the detection of allelic variants using proprietary methods. All testing was performed by Prometheus Therapeutics and Diagnostics (Prometheus Laboratories Inc, San Diego, CA). Patients in the IBS group had the following additional blood tests obtained: complete blood count, complete metabolic panel, erythrocyte sedimentation rate, C-reactive protein, and thyroid stimulating hormone.

Any celiac disease antibody (AGA IgG, AGA IgA, TTG, or EMA) above the reference range was considered to be an abnormal (positive) test result. All patients (regardless of indication for colonoscopy) with any positive celiac disease antibody test were offered esophagogastroduodenoscopy with at least 4 duodenal biopsies to confirm the diagnosis of celiac disease. These biopsy samples were obtained from the second and third portions of the duodenum using a forward viewing endoscope and additional biopsies, including from the duodenal bulb, were left to the discretion of the endoscopist. All biopsy samples were placed in 10% formalin, processed in accordance with each participating center's standard anatomic pathology specimen processing protocol, stained with H&E, and examined by staff pathologists at each institution. A blinded expert GI pathologist subsequently reviewed all duodenal biopsies obtained from individuals who had abnormal celiac antibodies. Patients were considered to have celiac disease if they had abnormal celiac antibody test results and also demonstrated small intestinal biopsy findings of villous atrophy and/or increased intraepithelial lymphocytes (IELs) based on the interpretation of the expert GI pathologist.