Abdominal Pain-Associated Functional Gastrointestinal Disorder Prevalence in Children and Adolescents with Celiac Disease on Gluten-Free Diet: A Multinational Study

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Objective To test the hypothesis that children with celiac disease (CD) on gluten-free diet are at increased risk of abdominal pain (AP) associated-functional gastrointestinal disorders (FGIDs).

Study design This was a multinational cross-sectional study performed from 2014 to 2015. Patients 4-18 years of age with CD on gluten-free diet for longer than 6 months were recruited from pediatric CD clinics in US and Italy. Control groups included siblings of children with CD (with normal tissue transglutaminase levels) and unrelated controls. Subjects or parents completed the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III.

Results Children (n = 289) were recruited (55% US, 45% Italy): 96 children with CD, 96 sibling controls, and 97 unrelated controls. Chronic AP was present in 30 (30.9%) subjects with CD, 22 (22.7%) sibling controls, and 21 (21.6%) unrelated controls ($P = .26$ patients with CD vs siblings; $P = .18$ patients with CD vs unrelated; $P = .96$ siblings vs unrelated). AP-FGIDs were present in 8 (8.2%) subjects with CD, 8 (8.2%) sibling controls, and 2 (2.1%) unrelated controls ($P = 1.00$ subjects with CD vs sibling controls; $P = .06$ subjects with CD vs unrelated controls; $P = .06$ sibling controls vs unrelated controls).

Conclusion This multinational study evaluated the prevalence of chronic abdominal pain and AP-FGIDs in the pediatric population with CD. We found that subjects with CD and controls have a similar prevalence of chronic AP and AP-FGIDs. This suggests that not all types of gastrointestinal inflammation result in AP-FGIDs in children. *(J Pediatr 2016;■■:■■-■■).*

Abdominal pain (AP)-associated functional gastrointestinal disorders (FGIDs) are highly prevalent worldwide.[1-7] In children, AP-FGIDs are associated with multiple comorbidities, poor quality of life,[8] and school absenteeism.[9] The costs associated with the care of children with AP-FGIDs are enormous. A study from the Netherlands estimated that the total annual medical and nonmedical costs per child with AP-FGIDs were in excess of €2500.[10] The costs associated with the workup of a single child with chronic AP in a tertiary hospital in the US exceed $6000.[11] The healthcare costs associated with the hospitalization of children with AP-FGIDs in the US have increased 3-fold from 1997 to 2009.[12] These studies stress the need to uncover the factors that predispose children to develop AP-FGIDs.

The pathogenesis of AP-FGIDs remains understood incompletely. Multiple studies in adult and pediatric patients have shown that AP-FGIDs frequently are preceded by intestinal inflammation. Pediatric studies have shown that 36% of children develop FGIDs following an acute gastrointestinal (GI) infection (postinfectious irritable bowel syndrome [IBS]).[13] Low-grade persistent inflammation and nerve sensitization are thought to explain the chronic symptoms.[14-17] Noninfectious causes of intestinal inflammation also have been associated with the development of AP-FGIDs. A high incidence of AP-FGID has been reported in children following Henoch-Schönlein purpura,[18] an autoimmune disease that frequently affects the GI tract. Other autoimmune diseases also have been associated with a high prevalence of AP-FIGDs. Thirty-five percent of adults with ulcerative colitis and 30% of adults with Crohn's disease on remission also have been diagnosed with IBS.[19,20]

The risk of developing AP-FGIDs following inflammatory GI diseases in children and adults seems to differ. Sixteen years after an acute gastroenteritis outbreak in Italy that affected school children and staff, children (but not adults) who contracted acute gastroenteritis had a greater prevalence of AP-FGIDs than those who were not exposed.[21] In contrast to the

AP	Abdominal pain
AP-FGID	Abdominal pain-associated functional gastrointestinal disorder
CD	Celiac disease
EGD	Esophagogastroduodenoscopy
FGID	Functional gastrointestinal disorders
GFD	Gluten-free diet
GI	Gastrointestinal
IBS	Irritable bowel syndrome
QPGS-RIII	Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III
tTG-IgA	Tissue transglutaminase immunoglobulin A

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high prevalence of IBS in adults with inflammatory bowel disease, only 6%[22,23] of children with Crohn's disease and 11% of children with ulcerative colitis[22] have symptoms of IBS.

Studies in adults have shown that patients with celiac disease (CD) who adhere to a gluten-free diet (GFD) are at increased risk of GI symptoms; 35% of patients with CD continued to experience AP discomfort, and 22% experienced diarrhea after 5 years of a GFD.[24] This finding would suggest that adults with both CD and inflammatory bowel diseases follow a similar pattern of frequent and chronic GI symptoms despite treatment.

We previously compared 46 children with CD on a GFD with controls (siblings without CD), and the study failed to show a difference in AP and AP-FGIDs between both groups.[25] These results seemed to contradict the study conducted in adults with CD; however, the former study did not include a healthy control group. A subsequent study has shown that individuals without CD but with IBS who had human leukocyte antigen (HLA) DQ2 and DQ8 genotypes were at risk of intestinal dysmotility.[26] Siblings of children with CD are at greater risk than the general population of having the HLA-DQ2 and HLA-DQ8 genotypes, which raises the question as to whether the results of the pediatric study comparing children with CD with their siblings would have been different if we had selected a control group that was not part of the same family. The dearth of studies characterizing the symptoms of non-CD siblings of children with CD precluded us from definitive conclusions.

We conducted a large, international collaborative study to compare the prevalence of AP and AP-FGIDs in 3 groups of children: children with CD on a GFD, sibling without CD, and unrelated controls. We hypothesized that children with CD on a GFD would have a significantly greater prevalence of chronic AP and AP-FGIDs than unrelated controls.

Methods

This international cohort study was conducted during 2014-2015 at 3 university hospitals in 3 cities: Chicago (US) and Messina and Verona (Italy). The study included 3 groups of 4- to 18-year-old children and adolescents: (1) children with CD on a GFD for more than 6 months; (2) sibling controls without CD; and (3) unrelated controls. The Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III (QPGS-RIII) was completed for each subject who consented to the study. The QPGS-RIII has been used successfully to identify AP-FGIDs in children according to the Rome III criteria.[27] The questionnaire includes questions on frequency, intensity, location, and duration of GI symptoms. According to the QPGS-RIII criteria, AP-FGIDs include functional dyspepsia, IBS, abdominal migraine, functional AP, and functional AP syndrome. The QPGS-RIII was completed as designed with parents completing the parent-report version for children aged 4-9 years and children aged 10 years and older completing the self-report version themselves. A validated Italian version was used in the centers in Italy.[28] The study was approved by the institutional review board of each participating hospital.

Families of children with CD who received care at the University of Chicago Celiac Disease Center in Chicago, US, and at the University of Messina Pediatric Gastroenterology Department in Messina, Italy, were invited to participate in the study. The diagnosis of CD was confirmed by chart review (history of elevated serum tissue transglutaminase immunoglobulin A [tTG-IgA] and confirmation by endoscopic esophagogastroduodenoscopy [EGD] with multiple biopsies from the duodenal bulb and second portion of the duodenum). All children with CD reported adherence to the GFD and had decreasing tTG-IgA values from the time of diagnosis. GFD education was provided by a nutritionist after diagnosis for each patient, and nutritionists remained readily available at both centers for follow up.

The closest sibling of the index case of the same sex with negative workup for CD served as control (normal tTG-IgA antibody levels and duodenal biopsies if an EGD was done). If no siblings of the same sex were available, the next sibling closest in age was invited to participate. Siblings without CD (normal tTG-IgA antibodies and/or EGD findings) from other families who had a child with CD were invited to participate to account for families with an only child with CD. Unrelated controls were recruited randomly among children without siblings with CD that consulted for a well child visit or non–GI-related complaint at the emergency department or general pediatric clinic in Chicago, US, and from a primary care clinic in Verona, Italy. Children with developmental delay were excluded from participating in the study.

Children who met strict criteria for AP-FGIDs according to the QPGS-III were diagnosed with an AP-FGID. For the purpose of this study, children who had 2 months of AP as required by the Rome III criteria for the diagnosis of an AP-FGID but did not meet the frequency of symptoms required in the criteria were given a diagnosis of chronic AP.

Our previous study of CD and siblings with AP-FGID required a sample size of 44 subjects per group to demonstrate a significant difference between 2 groups (CD vs each control group) based on a power of 80% and an alpha of 0.05.[25] The sample size for this study was doubled empirically to improve the power of the study. Information to directly match patients with CD to siblings was not available for all families, so significance of proportions between groups was evaluated with χ^2 and Fisher exact tests. Relative risk was used as a measure of association between exposure to CD and primary outcome (CD and chronic AP and AP-FGIDs). Risk of presenting the primary outcome in the group with CD was compared with the same risk in those without CD.

Results

A total of 289 children participated in the study (96 with CD on a GFD, 96 sibling controls, and 97 unrelated controls); 53 subjects were recruited into each group from Chicago, 43 subjects were recruited into the CD and sibling groups from Italy, and 44 subjects were recruited into the unrelated control group from Italy (**Table I**). One subject in the Italian group with CD and their corresponding sibling were excluded because they

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