Abdominal Pain and Functional Gastrointestinal Disorders in Children with Celiac Disease

Miguel Saps, MD[1], Papa Adams, BS[1], Silvana Bonilla, MD[2], and Diana Nichols-Vinueza, MD[3]

Objective To assess whether patients with celiac disease (CD) are more likely than controls to develop abdominal pain (AP) and AP-associated functional gastrointestinal disorders (FGID) in long-term follow-up.

Study design In a retrospective study, data on children (3-22 years old) with CD diagnosed between 2000 and 2010 were obtained. Parents were contacted by telephone at least 6 months after the diagnosis of CD and invited to participate in the study. Consenting parents completed: (1) a telephone questionnaire on the presence of gastrointestinal symptoms; and (2) the parent report version of the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III for cases and selected controls.

Results Forty-nine cases (mean 11.3 years, 20 male participants) and 48 controls (mean 11.1 years, 24 male participants) were enrolled. Twelve children in the CD group (24.5%) and 7 children in the control group (14.6%) had AP at the time of the study ($P = .3$). Nine children in the CD group (18.3%) and 4 children in the control group (8.3%) met criteria for an AP-associated FGID according to the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III ($P = .23$).

Conclusion It was found that children with CD and controls have a similar risk of AP and AP-FGIDs. Methodologic limitations prevent generalization of results, but large prospective studies should confirm the findings. *(J Pediatr 2013;162:505-9)*.

Celiac disease (CD) and abdominal pain (AP)-associated functional gastrointestinal disorders (AP-FGIDs) including irritable bowel syndrome (IBS) and functional dyspepsia are common in adults and children.[1,2] The diagnosis of AP-FGIDs and CD can pose some clinical challenges. The clinical presentation of CD is frequently atypical and there are no biologic markers to diagnose AP-FGIDs. Because the symptoms of CD such as AP, diarrhea, and bloating[3] often imitate those of IBS and functional dyspepsia, CD can be misdiagnosed as an AP-FGID.[4,5] Studies on prevalence of CD in adult patients with IBS have shown conflicting results. Although some studies found an association between these 2 conditions,[6] others did not.[7] Studies also have found a high prevalence of CD among adult patients with dyspeptic symptoms.[8-10] The current evidence in pediatric literature is limited. Two studies found only one case of CD among >200 children studied.[11,12] All the aforementioned studies provide relevant data on the relation of AP and AP-FGIDs and CD and underscore the importance of their identification at the time of diagnosis for appropriate treatment.[13,14] None of these studies investigated the long-term relationship of CD and AP-FGIDs. Understanding whether patients diagnosed with CD suffer from AP at long-term follow-up has potential important implications for research and clinical care. The pathogenesis of AP-FGIDs is incompletely understood.[15] Advancing the knowledge on the possible relation of CD and AP-FGIDs may increase our understanding of the pathophysiology and pathogenesis of FGIDs. Patients with inflammatory gastrointestinal conditions (infectious and noninfectious) are at higher risk of developing AP-FGIDs. Patients with IBS with and without a recent history of infection (postinfectious IBS and nonspecific IBS, respectively) show low-grade inflammatory infiltration in biopsies.[16] Studies in children have shown persistent AP and AP-FGIDs including IBS and dyspepsia several years after an acute gastrointestinal infection or immune conditions affecting the gastrointestinal tract.[17,18] CD is another example of an immune-mediated enteropathy characterized by T-lymphocyte–mediated inflammatory injury of the small intestinal mucosa. Demonstrating that patients with CD are at increased risk of developing AP-FGIDs several months or years after commencement of treatment would suggest that the development/persistence of symptoms could outlast the initial inflammation and that various inflammatory pathways may lead to a common phenotype—a concept that may help in the understanding of the pathogenesis of FGIDs.[19-21] Finding that patients previously diagnosed with CD continue to complain of AP has the potential to impact clinical care by reducing unnecessary testing and the possible mistrust of the child's compliance that may arise from frequent complains of AP.[22-25]

AP	Abdominal pain
AP-FGIDs	Abdominal pain-associated functional gastrointestinal disorders
CD	Celiac disease
EGD	Endoscopic gastroduodenoscopy
FGID	Functional gastrointestinal disorder
IBS	Irritable bowel syndrome
QPGS-RIII	Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III Version
TTG	Tissue transglutaminase

From the [1]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Children's Memorial Hospital, Feinberg School of Medicine, Northwestern University, Chicago, IL; [2]Division of Pediatric Gastroenterology, Hepatology and Nutrition, The Floating Hospital for Children, Tufts University Medical Center, Boston, MA; and [3]Deparment of Pediatrics, Universidad del Valle, Cali, Colombia

The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2012.08.032

We conducted a study to assess whether patients with CD are more likely than controls to develop AP and AP-FGIDs in long-term follow-up. We hypothesized that children with CD would be at higher risk of developing FGIDs.

Methods

Data on children (3-22 years old) with CD diagnosed at Children's Memorial Hospital between 2000 and 2010 were obtained. Charts were reviewed and the pathologic diagnosis of CD was confirmed in all cases. Children who had a wrong diagnosis or developmental delay and those from non–English-speaking families were excluded. Parents were contacted by telephone at least 6 months following the diagnosis of CD and invited to participate in the study. Consenting parents completed: (1) a telephone questionnaire on the presence of gastrointestinal symptoms; and (2) the parent report version of the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III (QPGS-RIII). The QPGS-RIII is a validated age-appropriate instrument commonly used to facilitate the diagnosis of FGIDs in children and adolescents.[26] The QPGS-RIII established: (1) a minimum time criterion of 2 months to characterize an AP case as an AP-FGID; and (2) specific criteria for each category of AP-FGIDs (IBS, functional AP, dyspepsia, and abdominal migraine). For the purpose of this study, we considered children meeting Rome time criterion of AP but not meeting rest of criteria for a specific AP-FGIDs as having chronic AP and those meeting all criteria were classified as AP-related FGIDs. The presence of AP was assessed by the following question: "Has your child complained of AP in the past 2 months?" (yes/no). Parents who reported the presence of AP were asked to complete the QPGS-RIII, which includes questions addressing the frequency, intensity, location, and duration of AP symptoms. Due to similar genetic and environmental background, the closest sibling of the patient who was of the same sex without history of CD and tissue transglutaminase (TTG) antibody or negative endoscopic gastroduodenoscopy (EGD) served as control. If no siblings of the same sex were available, the next child in kinship was selected as control. When a child in the study group had no siblings, another sibling or cousin from one of the families who had normal TTG and/or EGD results served as control. Sample size calculation was conducted to determine a sufficient sample size using an α of 0.05 and a power of 0.80. Sample size estimation found that 44 children in each arm were needed. Significance between groups was evaluated using relative risk and Fisher exact tests. Descriptive statistics were calculated using Statistical Package for Social Sciences version 11.5 for Windows (SPSS Inc, Chicago, Illinois). All studies were approved by the Institutional Review Board of Children's Memorial Hospital.

Results

Forty-six families participated in the study (43 families had 1 child with CD and 3 families had 2 children with CD). Forty-nine cases (mean 11.3 years, 20 male participants) and 48 controls (mean 11.1 years, 24 male participants) were enrolled; 43 of the 49 children with CD had at least 1 sibling who was included as a control in the study (**Figure**). For 16 patients who lacked a sibling control, a second sibling was recruited in 13 cases and a cousin in 2 cases. Twenty-two patients who were evaluated for CD and had a negative workup but were registered in the database as having CD were excluded due to a wrong diagnosis. Mean interval time since the diagnosis of CD was 3.7 years (range 0-17 years). Twelve children in the celiac group (24.5%) and 7 children in the control group (14.6%) had AP at the time of the study (P = .3). Relative risk of having AP in long-term follow-up in children with CD compared with controls was 1.68 (95% CI 0.72-3.90). Time to follow-up from time of diagnosis in CD patients reporting AP was 3.8 versus 3.7 years in those not reporting AP (nonsignificant). Similarly, there was no significant difference in the prevalence of AP when data on children in the CD group were compared with the data on their siblings (P = .4). Nine children in the CD group (18.3%) and 4 children in the control group (8.3%) met criteria for an AP-FGID according to the QPGS-RIII (P = .23). Children in the CD group who had an AP-FGID were diagnosed as having IBS (n = 3), functional dyspepsia (n = 2), abdominal migraine (n = 2), and functional AP (n = 2). Children in the control group meeting diagnostic criteria for AP-related FGIDs were diagnosed as having functional AP (n = 3) and IBS (n = 1) (**Table I**). Characteristics of AP in children with CD and controls are provided in **Table II**.

One year after the study was completed, we attempted to contact for a second time all families who had siblings with AP symptoms to assess their progress. We were able to reach 6 of 7 families. All children had persisting symptoms. In the interim, 4 families had consulted a gastroenterologist, who recommended repeat serology testing or EGD, which had normal results in all cases. One family who provided 2 siblings for the study reported that they were planning on

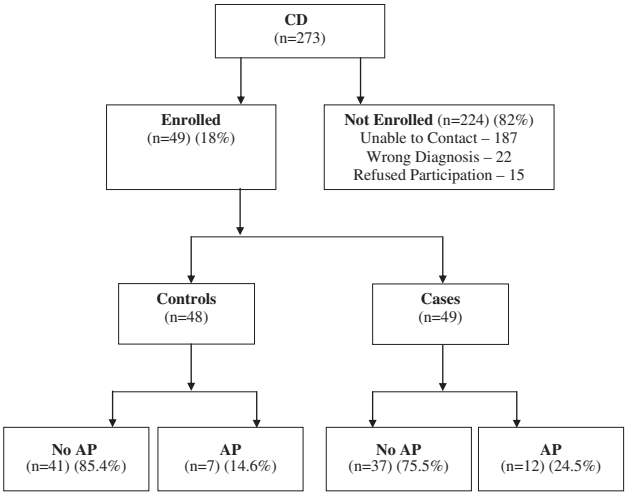

Figure. Flow chart of recruitment and outcomes.