Increased Prevalence of Celiac Disease Among Pediatric Patients With Irritable Bowel Syndrome: A 6-Year Prospective Cohort Study

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IMPORTANCE Recurrent abdominal pain is a prevalent health issue in childhood. Clinical criteria (ie, the Rome criteria) have been established to aid diagnosis. Studies of adults have shown an increased prevalence of celiac disease among patients with irritable bowel syndrome (IBS); few data are available with regard to children.

OBJECTIVE To assess the prevalence of celiac disease among children with abdominal pain-related functional gastrointestinal disorders classified according to the Rome criteria.

DESIGN, SETTING, PARTICIPANTS Six-year (2006-2012) prospective cohort study conducted in a tertiary referral center for the diagnosis and follow-up of gastrointestinal disorders in southern Italy (ie, Bari, Italy). A total of 992 children (42.8% male; median age, 6.8 years) consecutively referred for recurrent abdominal pain by their primary care physicians without previous investigation were evaluated.

EXPOSURE Patients were classified according to Rome III criteria as having IBS, functional dyspepsia, functional abdominal pain, or abdominal migraine.

MAIN OUTCOMES AND MEASURES Prevalence of celiac disease in each category of abdominal pain-related functional gastrointestinal disorder. Concentrations of IgA, IgA antitissue transglutaminase, and endomysial antibodies were measured, and a duodenal biopsy was performed in case of antibody positivity.

RESULTS A total of 992 children were evaluated: 270 were classified as having IBS, 201 as having functional dyspepsia, and 311 as having functional abdominal pain, and 210 children were excluded from the study because they had an organic disorder or some other functional gastrointestinal disorder (not related to abdominal pain). Serologic testing was performed for all 782 children included in the study, and 15 patients tested positive for celiac disease (12 of 270 patients with IBS [4.4%], 2 of 201 patients with functional dyspepsia [1%], and 1 of 311 patients with functional abdominal pain [0.3%]). Children presenting with IBS have a 4 times higher risk of having celiac disease than children without IBS (odds ratio, 4.19 [95% CI, 2.03-8.49]; P < .001).

CONCLUSIONS AND RELEVANCE The prevalence of celiac disease among children with IBS is 4 times higher than among the general pediatric population. Rome III classification of abdominal pain-related functional gastrointestinal disorders might help to select children who deserve screening for celiac disease.

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current abdominal pain is a disorder that affects 10% to 15% of school-aged children and has a significant impact in clinical practice, accounting for more than 50% of the consultations in pediatric gastroenterology and 2% to 4% of all general pediatric office visits.1,2

The Rome criteria are symptom-based functional disease criteria developed by a panel of experts in an attempt to reach a positive diagnosis in the presence of functional gastrointestinal disorders (FGIDs). The Rome III criteria identify 4 diagnostic symptom-based categories of abdominal pain-related FGIDs: irritable bowel syndrome (IBS), functional dyspepsia, childhood functional abdominal pain, and abdominal migraine (eTable in Supplement).3 A technical report by the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition on chronic abdominal pain states that most children are unlikely to require diagnostic testing and recommends making a positive diagnosis on the basis of a clinical criteria combined with a normal physical examination and the absence of alarming symptoms; therefore, few investigations have been recommended, and they do not routinely include the exclusion of celiac disease.4

The challenge for the clinician is to exclude organic abnormality on the basis of history, clinical examination, and absence of alarming features in order to avoid the morbidity of a missed diagnosis, and therefore a pragmatic approach needs to be followed.

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten (in genetically susceptible individuals) and results from the interaction between gluten and immune, genetic, and environmental factors.5 The prevalence of celiac disease is as high as 1% in European countries,6 and its clinical presentation can include a wide spectrum of insidious symptoms, including abdominal pain, although it is often asymptomatic.7

Just over a decade ago, Sanders et al8 showed that there was a significantly increased incidence of celiac disease among European patients with IBS who fulfil the Rome II diagnostic criteria. With an increased awareness of the symptoms suggestive of celiac disease, coupled with a low threshold for serological testing, Sanders et al8 were able to uncover a large portion of undiagnosed celiac disease among patients with IBS. A recent meta-analysis9 demonstrates a 4-fold higher prevalence of celiac disease among adults with IBS, whereas few data are available with regard to children.10-13 The aim of the present study was to assess the prevalence of celiac disease in each symptom-based category of abdominal pain-related FGID diagnosed according to the Rome III criteria.

Methods

Study Population

This was a prospective observational cohort study conducted between 2006 and 2012 at the pediatric department of the university hospital of Bari, Italy, that is the tertiary referral center for the diagnosis and follow-up of gastrointestinal disorders in our region, covering an estimated population of 1,400,000 children, with more than 6,000 children followed up in our gastrointestinal clinic. The study population was composed of pediatric patients consecutively referred for recurrent abdominal pain by their primary care physicians without previous investigation.

All children were managed according to the Rome III criteria: at study entry, a medical evaluation (which included reviews of the clinical history, medical records from the referring primary care provider, and family and social history; a complete physical examination; and auxological evaluation) was performed. Baseline investigations included complete blood count; erythrocyte sedimentation rate; C-reactive protein, serum amylase, lipase, iron, and alanine aminotransferase concentrations; and urinalysis. In presence of alarming features and in relation to clinical symptoms, further investigations were performed in order to exclude organic disease, as appropriate.3 Patients were excluded if they had organic disease or some other FGID (not related to abdominal pain). Enrolled patients were interviewed by the same physician and classified according to the Rome III criteria as having IBS, functional dyspepsia, functional abdominal pain, or abdominal migraine.3

Diagnostic Procedures

To investigate celiac disease, serum concentrations of IgA, IgA antitissue transglutaminase, and endomysial antibodies were tested, and a duodenal biopsy was performed in case of elevated levels of antibodies. IgA antitissue transglutaminase antibodies were detected using a commercial sandwich-type enzyme immunoassay with human recombinant transglutaminase antigen as the substrate, and the results are considered positive if greater than 10 arbitrary units/mL of the antibody are detected (ORGENTEC Diagnostika). Endomysial antibodies were detected by indirect immune fluorescence using commercial kits (Euroimmun Italia Diagnostica Medica SRL).

To confirm the diagnosis of celiac disease, patients with a serologic test result positive for celiac disease underwent an upper endoscopy with multiple duodenal biopsies. The biopsy specimens were flattened, orientated, and mounted over small pieces of filter paper, immediately and completely placed in formalin, and processed according to standard procedures. All biopsy specimens were graded by the same pathologist according to the Marsh criteria.14

The final diagnosis of celiac disease was based on the test result being positive for IgA antitissue transglutaminase and endomysial antibodies in the presence of histological evidence of villous atrophy with crypt hyperplasia and an increase in intraepithelial lymphocytes on a gluten-containing diet. Class II HLA antigen typing (HLA-DRB1*01,15,16,03,04,11,12,13,14,07,08,09,10; HLA-DRB3*; HLA-DRB4*; HLA-DRB5*; and HLA-DQB1*01,02,03) was performed with the use of a polymerase chain reaction, sequence-specific oligonucleotide, a low-resolution molecular method.15

To assess whether the presence of abdominal pain was the only clue to suspect the diagnosis of celiac disease, we compared auxological (centiles of height and weight), nutritional (iron, ferritin, and albumin), and biochemical (serum glucose, liver function tests, and hemoglobin) markers between...
children with celiac disease and children without. Our study adhered to the Declaration of Helsinki and was approved by the institution's ethics review board; written informed consent from parents or legal representatives was obtained.

**Statistical Analysis**

With the assumption that celiac disease would be expected to occur in 4% of those with IBS, in 3% of those with functional dyspepsia, and in 1% of the general pediatric population, we calculated that a sample of 265 children with IBS and 490 children with functional dyspepsia would be required for the study to have 95% power based on a 2-sided type 1 error rate of 5%. Owing to the lack of literature on the prevalence of celiac disease among children with functional abdominal pain and children with abdominal migraine, no power calculations were possible. Data are presented as absolute numbers and percentages. The incidence rate and the prevalence rate of celiac disease are expressed as mean values and 95% CIs. For continuous variables, the Wilcoxon test was used for comparison of the mean values. For nominal variables, the χ² test or the Fisher exact test was used, as appropriate, to compare percentages and nominal variables. All statistical tests were 2-tailed and performed at the 5% level of significance. Data were analyzed with SPSS 13.0 software (SPSS Inc).

**Results**

A total of 992 patients 4 to 16 years of age (42.8% male; median age, 6.8 years) were referred to our hospital for the management of recurrent abdominal pain. Based on the Rome III criteria, 284 children underwent further examinations because of the presence of alarming features and/or in relation to clinical symptoms and/or alterations in biochemical/hematological parameters. An organic disorder was diagnosed for 126 of the 992 patients (12.7%): 55 had a gastroesophageal reflux disease, 42 had gastritis (of whom 16 had Helicobacter pylori infection), 18 had lactose intolerance, 9 had parasitosis, and 2 had inflammatory bowel disease. Other FGIDs (not related to abdominal pain), including constipation, were diagnosed for 84 children. Therefore, 782 of the 992 children (78.8%; 43.7% of whom were male; median age, 7.1 years) were classified according to the Rome III criteria in the different diagnostic subgroups: 270 children (34.5%) had IBS, 201 children (25.7%) had functional dyspepsia, and 311 children (39.8%) had functional abdominal pain (and functional abdominal pain syndrome) (Figure).

Fifteen of the 782 patients (1.9%) tested positive for IgA antitissue transglutaminase and endomysial antibodies, none of whom showed selective IgA deficiency. All of these patients underwent an endoscopy of the upper gastrointestinal tract, and duodenal biopsy specimens showed mucosal atrophy in all 15 patients (Type 3 lesion based on the Marsh criteria).

The prevalence of celiac disease in different diagnostic subgroups is summarized in Table 1. Considering that the highest prevalence rate of celiac disease in a large sample of an Italian pediatric population is 1.1% (35 of 3188 schoolchildren), the prevalence rate of celiac disease among children with IBS is significantly higher than expected (4.4%); children with IBS have 4 times higher risk of having celiac disease than the general pediatric population (P < .001; odds ratio, 4.19 [95% CI, 2.03-8.49]). Even considering the highest prevalence rate of celiac disease in a European population (in Finland, at 2.5% [161 of 6403 participants]), the prevalence of celiac disease among our children with IBS is still significantly higher than expected (P < .05; odds ratio, 1.80 [95% CI, 0.90-3.38]). The prevalence of celiac disease in the overall population of children with abdominal pain-related FGIDs, and in the 2 categories of func-
Both IBS and celiac disease are prevalent conditions that share a common set of symptoms. Previous studies indicated that individuals meeting diagnostic criteria for IBS might be at higher risk of having celiac disease compared with controls without IBS; however, the data are conflicting.

In a case-control study of 300 patients with IBS and 300 healthy controls, Sanders and colleagues\(^8\) reported that IBS was significantly associated with celiac disease (odds ratio, 7.0 [95% CI, 1.7-28.0]; \(P = .004\)). These results were confirmed in a second study by Sanders and colleagues\(^9\) of 1200 adults showing a prevalence rate of 3.3% of celiac disease among 123 patients with IBS compared with a prevalence rate of 1% in the overall population. Recently, Jadallah and Khader\(^10\) reported a prevalence rate of celiac disease among patients with IBS of 3.2% in Jordan, and similar rates are reported in a Turkish study\(^11\) and in an Iranian study.\(^12\) Not all clinical observations point in favor of this association. In a primary care setting, Locke et al\(^13\) reported no difference in the prevalence of celiac disease among 50 patients with IBS compared with controls. Van der Wouden et al\(^14\) reported that none of the 154 patients with IBS that they observed tested positive for endomysial antibodies, nor did any of them have histopathological findings consistent with celiac disease. El Salhy et al\(^15\) reported a 0.4% prevalence rate of biopsy-proven celiac disease among 968 patients with IBS from Norway, and Ozdil et al\(^16\) found no cases of celiac disease among 60 adult patients with IBS. Recently, in a case-control study of 492 adult patients with nonconstipated IBS, Cash et al\(^17\) reported a higher prevalence of positive serologic test results for celiac disease among patients with IBS than among controls (1.2% vs 0.4%), although this was not confirmed by duodenal biopsy evaluations.

In light of this uncertainty, Ford et al\(^18\) performed a systematic review and meta-analysis to estimate the pooled prevalence and the incremental odds of celiac disease among individuals meeting diagnostic criteria for IBS. Fourteen studies were identified comprising 4204 individuals, and it was concluded that the prevalence of biopsy-proven celiac disease among patients meeting diagnostic criteria for IBS was 4-fold higher than among controls without IBS.\(^9\)

No conclusive data are available for children because there are only a small number of reports available. Two studies\(^19,20\) were performed for children with recurrent abdominal pain defined according to the Apley and Nash criteria: Fitzpatrick et al,\(^21\) in a community-based case-control study, found no difference in the prevalence of celiac disease among 92 children with recurrent abdominal pain, whereas Saltik et al,\(^22\) in a letter, report a prevalence rate of celiac disease of 2.7% among 110 children. Another study\(^23\) reports a prevalence rate of celiac disease of 1.3% among Iranian children with functional abdominal pain classified according Rome III criteria. Recently, in a retrospective study, Chumpitazi et al\(^24\) reported a prevalence rate of 4.9% of celiac disease among children with a primary complaint of chronic abdominal pain.

The routine exclusion of a diagnosis of celiac disease for all patients with IBS is currently recommended by the National Institute for Health and Clinical Excellence in the United Kingdom,\(^25\) and this strategy has been proven to be cost-effective for a prevalence rate of celiac disease among patients with IBS higher than 1%.\(^26\) The absence of a uniform testing strategy

### Table 2. Auxological, Nutritional, Biological, and Hematological Markers for Children With Celiac Disease and Abdominal Pain–Related Functional Gastrointestinal Disorders vs Children With Abdominal Pain–Related Functional Gastrointestinal Disorders Only (Controls)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Patients With Celiac Disease (n = 15)</th>
<th>Controls (n = 767)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>7.5 (4.0-15.2)</td>
<td>6.8 (4.0-16.0)</td>
<td>.30</td>
</tr>
<tr>
<td>Weight centile</td>
<td>54.4 (33.0)</td>
<td>62.0 (25.0)</td>
<td>.80</td>
</tr>
<tr>
<td>Height centile</td>
<td>52.2 (32.0)</td>
<td>49.9 (23.0)</td>
<td>.80</td>
</tr>
<tr>
<td>Iron, μg/dL</td>
<td>75.3 (33.4)</td>
<td>44.3 (23.9)</td>
<td>.10</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>39.7 (21.7)</td>
<td>41.7 (21.5)</td>
<td>.99</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9 (0.2)</td>
<td>3.3 (1.7)</td>
<td>.80</td>
</tr>
<tr>
<td>Serum glucose, mg/dL</td>
<td>79.5 (8.1)</td>
<td>81.3 (9.4)</td>
<td>.99</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.0 (0.9)</td>
<td>12.3 (0.8)</td>
<td>.80</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>31.7 (11.5)</td>
<td>22.2 (9.5)</td>
<td>.03</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert iron to micromoles per liter, multiply by 0.179; to convert ferritin to picomoles per liter, multiply by 2.247; to convert albumin and hemoglobin to grams per liter, multiply by 10; to convert serum glucose to millimoles per liter, multiply by 0.0555; and to convert alanine aminotransferase to microkatal per liter, multiply by 0.0167.
for celiac disease among children with chronic abdominal pain has recently been pointed out by Chumpitazi et al,37,38 who have reported a high variation in frequency of celiac disease testing among physicians in a tertiary referral center. Herein, we report a 6-year prospective observational cohort study of 992 children consecutively referred for chronic abdominal pain by their primary care physicians without previous investigation. Our most important finding is that 4% of these children have celiac disease and that children with IBS, by dint of receiving more medical attention for gastrointestinal symptoms, are more likely to have undiagnosed celiac disease.

Living with untreated celiac disease is associated with an increased risk for extensive negative health consequences. 39-40 Considering that the estimated delay, from symptoms to diagnosis, is about 10 years,32-34 that there are still 5 to 10 undiagnosed cases for every diagnosis,6 and that occult celiac disease seems to start in childhood, even in those whose symptoms are subsequently diagnosed when they are adults,35 the addition of a new category to the case-finding strategy might be of great help. A significant delay in the diagnosis of celiac disease in childhood might increase the risk of complications such as osteopenia, short stature, delayed puberty, infertility, and intestinal lymphoma in late adulthood. Weiss at al36 demonstrated that the delayed diagnosis of celiac disease had an influence on height among men, with an inverse correlation between the age at diagnosis and the final attained height. Reduced bone mineral density of the total body skeleton has been shown to be a common complication of untreated celiac disease,37,38 and considering that a gluten-free diet promotes a rapid increase in bone mineral density, a significant recovery of bone mineralization in children can be reached before the age of peak bone mass.39 This beneficial effect on bone mineral density is peculiar to children and does not occur in adults,40 reinforcing the need for an early diagnosis.

There are limitations to our study. We deliberately decided not to have a control group because data on the prevalence of celiac disease among large samples of Italian children already exist, and with an accuracy that we could not have achieved. These large epidemiologic studies report prevalence rates of celiac disease ranging from 0.54%40 to 1.09%.37 Considering the highest rate, we have still been able to demonstrate a significant increased risk of celiac disease among children with IBS. Conducting a study comparing IBS and non-IBS groups in the general population would require thousands of patients and is not likely to ever be done because of its impracticality and high cost. Our study may suffer from referral bias because the patients in our study were referred to a specialty clinic, so attention should be paid to translating our findings into primary care. Finally, our study did not prove an increase in prevalence of celiac disease outside of IBS because we do not have sufficient power to make negative statements regarding other abdominal pain–related FGIDs.

The strengths of the present study are that, to the best of our knowledge, it is the first study of a large pediatric population to investigate the association between celiac disease and each of the 4 diagnostic symptom-based categories of abdominal pain–related FGID according to the Rome criteria and to demonstrate that IBS-related symptoms might be the only clue to suspect a diagnosis that would otherwise have been missed. Translated into daily practice, this would mean that the presence of at least 2 months of abdominal pain relieved by defecation and/or associated with a change in frequency and/or form of stool should alert the physician to screen the patient for celiac disease.

Conclusions

Recent data have shown that IBS-type symptoms occur more frequently among patients with celiac disease who are on a gluten-free diet than among controls.41 Therefore, determining whether patients with IBS who receive a diagnosis of celiac disease continue to present with symptoms during long-term follow-up has potential important implications for future prospective studies.

The identification of IBS as a high-risk condition for celiac disease might be of help in pediatric primary care because it might have become routine to test for celiac disease indiscriminately in all children with recurrent abdominal pain, although our finding suggests that the screening should be extended only to those with IBS. This new approach might have important implications for the cost of care because it has been estimated that in children with FGIDs, screening tests are common, costs are substantial, and the yield is minimal.42 Considering that, in our series, 1 in 23 children with IBS has celiac disease, the immediate testing for celiac disease would result in a significant reduction in the cost of diagnostic procedures.

The high prevalence of celiac disease found among individuals affected by numerous common disorders, including type 1 diabetes mellitus, osteoporosis, Down syndrome, and Turner syndrome,43 that have been included in celiac disease screening programs7 should be an endorsement for the conducting of large multicenter studies to confirm the association between IBS and celiac disease in order to implement guidelines to prevent the unnecessary delay in the diagnosis of celiac disease in the future.
Celiac Disease Among Pediatric Patients With IBS

REFERENCES