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ORIGINAL ARTICLE

Frequency of Celiac Disease in Children with Peptic Ulcers

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Abstract

Aim The aim of the present study is to investigate the frequency of celiac disease in children with peptic ulcers and to compare it with that of non-celiac peptic ulcers in terms of clinical and laboratory values.

Methods Upper gastrointestinal endoscopy was performed in 1769 patients at the Department of Pediatric Gastroenterology, The Faculty of Medicine, Cukurova University, Turkey, between January 2012 and January 2017. These cases consisted of subjects presenting with various GIS symptoms and indicated for endoscopy (with chronic diarrhea, delayed growth and development, abdominal pains, GIS bleeding, etc.). The levels of immunoglobulin A (IgA) serum anti-tissue transglutaminase antibodies, IgA anti-endomysial antibodies (EMA), and IgA serum were estimated in the patients with peptic ulcers.

Results Celiac disease was diagnosed with serology, endoscopy, and histopathology in 250 (14%) of all cases undergoing endoscopy. Peptic ulcers were diagnosed in 74 patients (4.2%) of all cases undergoing endoscopy. tTGA and EMA (+) levels were determined in 22 (29%) of the 74 patients with peptic ulcers, and then the presence of peptic ulcers was investigated in the upper gastrointestinal system using gastrointestinal endoscopy, followed by histopathological confirmation of celiac disease. HP infection was present in 14 (63%) of the patients with celiac disease and in 23 (44%) of non-celiac peptic ulcers; the difference was not statistically significant ($p = 0.12$). In the total ulcer group, 10.8% (8/74) of patients with celiac peptic ulcers were negative for HP infection, whereas 21% (8/37) of HP-negative patients with ulcers had celiac disease.

Conclusion There exists a high risk of celiac disease in children with peptic ulcers. We thus recommend celiac disease to be investigated, particularly in HP-negative patients with peptic ulcers but with no history of NSAID use.

Keywords Celiac disease · Peptic ulcers · Childhood · *H. pylori*

Introduction

Peptic ulcers are lesions in the gastric mucosa or in the proximal intestine and extend as far as the muscularis mucosae. They occur in areas exposed to acid and pepsin. Classic peptic ulcer disease is a chronic recurrent condition characterized by impaired wound healing [1].

Although not as common as in adults, peptic ulcers are frequently detected in children [2]. This disease results from the disturbance of equilibrium between inimical elements [such as *Helicobacter pylori* (HP), gastric acid, nonsteroidal anti-inflammatory drugs (NSAIDs), and pepsin] and protective elements (such as mucus, prostaglandins, bicarbonate, and mucosal blood supply).

HP infection is the most common cause of primary duodenal ulcers in children with a reported global prevalence of 1.2–86% [3, 4]. Cinar et al. [5] reported a prevalence of 49% in pre-school and school children in Turkey, whereas, in an

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unpublished study at our clinic, it was detected in 27.3% of children with dyspeptic symptoms.

Several recent studies have reported an increase in the prevalence of non-HP non-NSAID peptic ulcer disease in adults [6–8], and one study determined a prevalence of 1 in 3 for non-HP non-NSAID peptic disease, the majority being idiopathic. The authors also described these as emerging earlier than HP-related peptic ulcers [9].

Celiac disease is an immune-related enteropathy in individuals with genetic gluten sensitivity that induces both gastrointestinal and non-gastrointestinal symptoms [10]. The prevalence of celiac disease varies between 1:100 and 1:200 in Europe [10–12], whereas it is 0.47% in Turkey [13].

Damage to the duodenal and jejunal mucosa is observed in most cases of celiac disease. In the literature, comorbid HP infection, celiac disease, and celiac disease-associated peptic ulcers (celiac peptic ulcers) have been reported [14], whereas the prevalence of celiac peptic ulcer cases has been observed in a case report [15] and a few studies [16–18]. The purpose of the present study is to investigate the frequency of celiac disease in children with peptic ulcers and to compare it with that of non-celiac peptic ulcers in terms of clinical and laboratory values.

Methods

Patient Population

Upper gastrointestinal endoscopy was performed in 1769 patients at the Department of Pediatric Gastroenterology, The Faculty of Medicine, Çukurova University, Turkey, between January 2012 and January 2017. These cases consisted of subjects presenting with various GIS symptoms and indicated for endoscopy (with chronic diarrhea, delayed growth and development, abdominal pains, GIS bleeding, etc.).

Investigations

The levels of immunoglobulin A (IgA) serum anti-tissue transglutaminase antibodies (tTGA), IgA anti-endomysial antibodies (EMA), and IgA serum were estimated in the 74 patients with peptic ulcers. The IgA tTGA and IgA EMA levels were measured using microELISA (Orgentec, Germany) and Generic Assays (Germany), respectively. The lower limit of tTGA positivity was 20 U/mL. tTGA values in our patients were 85–900 U/mL, whereas EMA values were 60–314 U/mL. Endoscopy was performed by an experienced endoscopist using the Pentax EG-2730 K Gastroscope (Pentax, Tokyo, Japan). Gastric and duodenal biopsy specimens were stained with hematoxylin and eosin and examined for the presence of HP infection and celiac disease. The parents of patients were informed about the procedures in advance, and their informed consents were obtained.

Duodenal biopsy specimens collected from all patients were classified according to their Marsh type. Twenty-two patients with tTGA and EMA positivity and biopsy specimens compatible with celiac disease were considered to have celiac disease [Marsh 3A: six cases (celiac test negative in two cases); Marsh 3B: eight cases; Marsh 3C: 10 cases]. All patients diagnosed with celiac disease were started on gluten-free diets.

All patients with peptic ulcers were evaluated for the presence of HP infection and dyspeptic symptoms, NSAID use, transfusion requirements, mean corpuscular volume (MCV), and levels of ferritin, hemoglobin, vitamin B_{12}, folic acid, and 25-OH vitamin D.

The absence of such anomalies for some diseases in the patients were as follows: Zollinger–Ellison syndrome because of the absence of multiple ulcers; cytomegalovirus infection because of the absence of any finding associated with immune deficiency in patients' histories; systemic mastocytosis through the involvement of skin, bone, and bone marrow findings; and hyperparathyroidism through incompatibility of clinical and laboratory values, no history of short bowel syndrome, and no clinical or laboratory findings of cystic fibrosis.

All HP-positive patients were administered with 50 mg/kg/day amoxicillin in two doses (for 15 days), 14 mg/kg/day clarithromycin in two doses (for 15 days), 1 mg/kg/day lansoprazole in two doses (for 1.5 months), and 50 mg/kg/day sucralfate in three doses (1.5 months). HP-negative patients received only 1 mg/kg/day lansoprazole in two doses (1.5 months) and 50 mg/kg/day sucralfate in three doses (1.5 months). Control endoscopy was performed after 1.5 months for all patients, followed by an evaluation of their HP infection and celiac disease status.

Statistical Analysis

Statistical tests were performed using the Statistical Package for the Social Sciences (v.20.0) software (IBM, Armonk, NY, USA). The results are expressed as mean ± standard deviation. Chi square test and Student's *t* test were used for comparisons. A p value of < 0.05 was considered statistically significant.

Ethics

The protocol was approved by the Ethics Committee of the Çukurova University, Turkey.

Results

Patient Characteristics

No statistically significant difference was observed between patients with celiac ulcers and non-celiac peptic ulcers cases in terms of age or sex ($p > 0.05$). Higher frequencies of nausea, vomiting, eructation, abdominal pain, and presence of melena were observed in patients with non-celiac peptic ulcers, whereas significantly higher frequencies of developmental retardation and lethargy were observed in patients with celiac peptic ulcers ($p < 0.05$). No history of NSAID use was recorded in any case. Erythrocyte transfusion was required in three cases of non-celiac peptic ulcers (Table 1).

Table 1 Demographic characteristics, symptoms, NSAID use, and erythrocyte transfusion requirements in celiac and non-celiac peptic ulcer cases

	Celiac ($n=22$)	Non-celiac ($n=52$)	p
Famale/male	6/16	30/22	0.29
Age (year)	9.3 ± 4.3	11.5 ± 4.8	0.06
Nausea	1 (4%)	30 (57%)	**0.001**
Vomiting	0	33 (63%)	**0.001**
Stomachache	1(4%)	47 (90%)	**0.001**
Burp	0	13 (25%)	**0.01**
Melena	0	8 (15%)	**0.051**
Malaise	12 (55%)	3 (5%)	**0.001**
Failure to thrive	21 (95%)	4 (7%)	**0.001**
Distension	1 (4%)	3 (7%)	**0.001**
Use of NSAID	0	0	
Erythrocyte transfusion requirements	0	3 (5%)	

Significant values shown in bold

NSAID nonsteroidal anti-inflammatory drugs

Relation Between Prevalence of Celiac Disease and HP Infection

Celiac disease was diagnosed with serology, endoscopy, and histopathology in 250 (14%) of all patients undergoing endoscopy. Peptic ulcers was diagnosed in 74 (4.2%) of all patients undergoing endoscopy.

CD was determined in 22 (29%) of the 74 patients with peptic ulcers, while HP infection was present in 14 (63%) of the patients with celiac peptic ulcers and in 23 (44%) of non-celiac peptic ulcer cases. However, the difference was not statistically significant ($p = 0.12$) (Fig. 1).

In the total ulcer group, 10.8% (8/74) of patients with celiac peptic ulcers were negative for HP infection, whereas 21% (8/37) of HP-negative patients with ulcers had celiac disease.

HP infection was detected in 44 of 206 celiac patients without ulcers (44/228; 23%), with a statistically significant difference being observed between these patients and the celiac patients with ulcers ($p < 0.001$).

Characteristics, Treatment and Follow-Up of Peptic Ulcers

The majority of ulcers identified in the upper gastrointestinal tract were present in the bulbus (58/74 patients; 78%). Ulcers in the antrum alone were detected in 11 patients (15%), while ulcers in the antrum and bulbus were detected in five patients (7%) (Table 2). Ulcer size in patients with ulcers in the antrum and celiac disease was 1 × 1 cm. The majority of ulcers in the bulbus were in the form of multiple aphthous or millimetric ulcersations. Intestinal metaplasia was identified in three HP-positive celiac cases.

Control endoscopy was performed in all cases 1.5 months after the first endoscopy. By then, the ulcers had completely resolved in 72 patients, while persisting in the bulbus in two non-celiac ulcer patients.

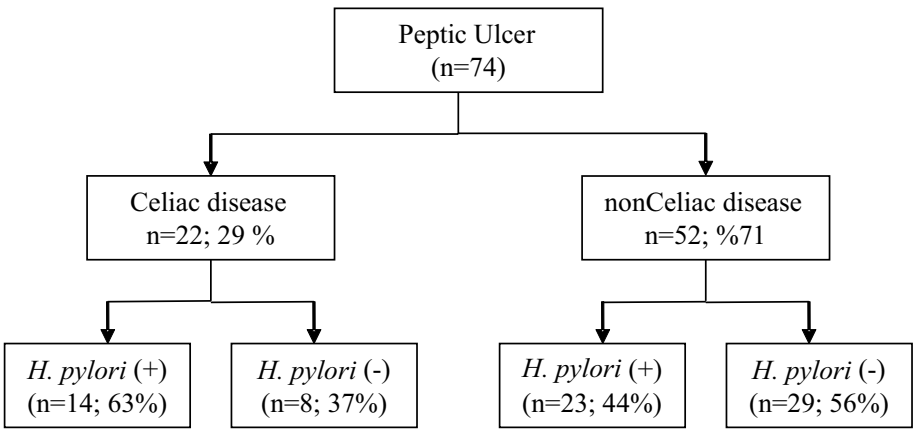


Fig. 1 Classification of cases with peptic ulcers in terms of celiac disease and *Helicobacter pylori* status

Table 2 Locations of ulcers in the gastrointestinal system of patients with peptic ulcers

	Celiac ($n=22$)	Non-celiac ($n=52$)
Antrum	3 (14%)	8 (16%)
Bulbus	15 (68%)	43 (82%)
Antrum + bulbus	4 (18%)	1 (2%)

Laboratory Characteristics of Cases with Peptic Ulcers

Hemoglobin, MCV, and ferritin levels were significantly low in the celiac ulcer group. No significant difference was determined between celiac ulcer and non-celiac ulcer patients in terms of other laboratory values (Table 3).

Discussion

Patients with celiac disease present with diverse clinical manifestations. For instance, celiac disease has been reported in association with hematological problems, such as iron-deficiency anemia and methemoglobinemia, neurological, endocrine, and autoimmune diseases [4, 10, 19].

An association between celiac disease and peptic ulcer disease has also been reported in a few cases [20, 21]; most of these being HP-positive. A prevalence of HP infection of 18.5–42% has also been reported in cases of pediatric celiac disease [22, 23]. Apart from ulcers in the stomach, ulcerations in the upper gastrointestinal system in celiac disease are usually observed in the jejunum and less commonly in the ileum [24, 25]. Baer et al. [26] identified ulcers during surgery in 47 patients with malabsorption syndrome, 22 of whom had celiac disease.

Ulcer development in celiac disease is generally reported to be multiple, chronic, and usually in the jejunum, with the involvement of the submucosa and muscularis propria [26]. In our subjects, peptic ulcers generally developed in the bulbus and were diffusely distributed.

Celiac disease was determined in 29% of the patients with peptic ulcers in our study, which is a very high proportion. HP infection was positive in most of these cases (63%), while it was negative in 21% of the celiac patients without peptic ulcers; the difference between these two groups was found to be statistically significant. This observation also suggests that a large proportion of ulcers determined in celiac disease are associated with HP infection and that no underlying cause other than celiac disease could be identified in eight patients with peptic ulcers who were HP-negative. Levine et al. [18] detected duodenal ulcers in the duodenal bulb in seven patients, two of whom were HP-positive. HP infection was negative in three patients in whom gastric ulcers were detected. A gluten-free diet and triple therapy for the HP-positive patients was prescribed, with resolution observed in 87% of the patients.

In all our subjects, the ulcers disappeared at control endoscopy after 1.5 months after treatment with a gluten-free diet and proton pump inhibitors (PPI) + sucralfate therapy. We could not ascertain whether these cases resolved as a result of the gluten-free diet or the PPI + sucralfate therapy. However, as it was inappropriate to administer diet therapy alone in children, we administered the PPI + sucralfate therapy as well. We believe that both treatments were effective in eliciting the response to treatment.

This study has some limitations. First, differential diagnosis was performed with anamnesis alone in the etiology of ulcers in HP-negative cases; no additional tests were performed. None of the cases had a history of chronic underlying disease. No history of NSAID use was reported in the previous 15 days.

Another limitation of this study is that a standard triple therapy was not administered in HP-positive patients with celiac disease; rather, only strict gluten-free therapy was administered. As it seemed unethical to treat ulcer patients with a diet therapy alone, PPI + sucralfate therapy

Table 3 Laboratory values in celiac and non-celiac patients

	Celiac ($n=22$)	Non-celiac ($n=52$)	p
Hemoglobin (g/dL)	10.6 ± 1.6	11.8 ± 2.2	**0.02**
MCV (fL)	72 ± 7.2	79.3 ± 7.9	**0.002**
Iron (µg/dL)	31.8 ± 21.7	38.7 ± 26.1	0.2
TIBC (µg/dL)	376 ± 42	350 ± 95	0.2
Ferritin (ng/mL)	11.2 ± 7.5	19 ± 16	**0.04**
Vitamin B_{12} (pg/mL)	257 ± 117	223 ± 134	0.3
Folat (ng/mL)	8.5 ± 4.4	10.2 ± 5.8	0.2
Bone mineral density (Z score)	− 0.7 ± 0.4	0.5 ± 0.4	0.2
25 (OH) vitamin D (ng/mL)	21.4 ± 12.3	21.5 ± 8.5	0.9

Significant values shown in bold

MCV mean corpuscular volume, *TIBC* total iron-binding capacity

was provided together with the diet therapy. With this treatment, the ulcers in eight HP-negative patients resolved after 1.5 months, as confirmed by gastrointestinal endoscopy.

Notably, almost all other previous studies had retrospectively examined dyspeptic syndromes in celiac patients. In contrast, the present study is a prospective study that investigated celiac diseases in all patients presenting with peptic ulcers. We determined celiac disease at a level of 10.8% in HP-negative patients with no NSAIDs association.

Various theses have been published concerning the pathophysiology of ulcer development in patients with celiac disease. Tissue transglutaminase 2 has been reported to compromise several stages of angiogenesis [27, 28]. Veres et al. [29] determined plasminogen I deficiency in a patient with celiac disease and duodenal ulcers. Gluten-related mucosal damage has also been reported in such cases. Intense chronic inflammatory cell infiltration has been shown to cause flattened mucosa in small bowel ulceration and to be immunologically active [30]. As a result, easy ulcer development has also been reported. We believe that bicarbonate secretion impairment due to mucosal damage and elimination of acidity could also have affected the development of ulcers in celiac patients of this study. However, none of these hypotheses can adequately explain the pathogenesis; otherwise, ulcers would have been detected in the majority of celiac patients.

Abdominal and gastric pain occurred in only one celiac patient with an ulcer, which was most unexpected. The literature does not report a single case of functional disorder in association with pain transmission in celiac patients. We potentially attributed this unexpected result to damaged mucosa and shallow superficial ulcers. On the other hand, extremely low levels of hemoglobin, MCV, and ferritin in the celiac group were found, as expected, due to absorption impairment.

In conclusion, there exists a high risk of celiac disease in children with peptic ulcers. We thus recommend celiac disease to be investigated, particularly in HP-negative patients with peptic ulcers but with no history of NSAID use.

Key Messages

1. What is the current knowledge
   - Damage to the duodenal and jejunal mucosa is observed in most cases of celiac disease.
   - In the literature, comorbid HP infection, celiac disease, and celiac disease-associated peptic ulcers (celiac peptic ulcers) have been reported, whereas the prevalence of celiac peptic ulcer cases has been observed in a case report and a few studies
2. What is new here
   - There exists a high risk of celiac disease in children with peptic ulcers.
   - Celiac disease should be investigated, particularly in HP-negative patients with peptic ulcers but with no history of NSAID use.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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