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Prevalence of *Helicobacter pylori* Infection in Pediatric Patients With Celiac Disease

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Abstract

BACKGROUND/AIMS: Celiac disease (CD) has been reported to be associated with chronic gastritis and immunological disorders. The aim of the study was to determine the association between *Helicobacter pylori (H. pylori)* infection and CD in children.

MATERIALS AND METHODS: Two hundred and two patients with CD aged from 6 months to 17 years (mean: 7.12±4.64), and 209 age- and sex-matched children without CD were screened for *H. pylori* infection.

RESULTS: Endoscopic appearance revealed significant differences between those patients with CD and the controls both in the antrum and the corpus ($p<0.001$). Those patients with CD had more frequent superficial gastritis than the control group. Panmucosal gastritis was common in the *H. pylori*-positive patients with CD. Lymphoid aggregates were significantly higher in the *H. pylori*-positive and *H. pylori*-negative patients with CD ($p<0.001$).

CONCLUSIONS: The prevalence of *H. pylori* infection was not different between those pediatric patients with CD or without CD.

Keywords: Celiac disease, children, *H. pylori*, infection, endoscopy

INTRODUCTION

Celiac disease (CD) is an immune-mediated disease characterized by malabsorption due to villous atrophy of the proximal small intestine triggered by gluten. The prevalence of CD in Turkey has been reported to be 0.47%.[1]

It has been reported that 70-80% of adults and 30%–56.6% of children in Turkey are infected with *Helicobacter pylori (H. pylori)*.[2] As *H. pylori* is the leading cause of chronic gastritis (more than 90%),[3] it is speculated that the prevalence of *H. pylori* in patients with CD might be high. The autoimmune response against *H. pylori* can be a factor in the development of CD in patients infected with this bacterium.[4]

There are studies reporting no significant change in the prevalence of *H. pylori* in patients with CD when compared with the normal population and also no relationship between *H. pylori* and the natural course of CD.[5-11] An increased prevalence of *H. pylori* in those patients with CD has been established in some studies,[12] and a decreased prevalence in others.[13-15] In this study, the prevalence of *H. pylori* infection in pediatric patients with CD was determined and compared with the prevalence in children without CD.

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MATERIALS AND METHODS

A total of 202 children with diagnosed CD and followed up between 2000 and 2015 at a division of pediatric gastroenterology were evaluated prospectively and compared with 209 controls who were recruited from children who had diagnostic upper gastrointestinal endoscopy for complaints such as abdominal pain, weight loss, growth retardation after CD had been excluded. The control group consisted of patients who were thought to have organic abdominal pain due to the fact that they had morning hunger pains, especially those who woke up during the night, and who had undergone endoscopy.

The diagnosis of CD was based on the criteria declared by ESPGHAN.[16] The diagnosis was made only histopathologically. The modified Marsh classification was used for grading the histopathological changes of the small intestinal biopsies.[17]

Endoscopic Evaluation

Endoscopy was performed with an Olympus Q260 or Olympus GIF P30 (Olympus, Tokyo, Japan). Intravenous (0.1 mg/kg) or rectal (0.5 mg/kg) midazolam was given 30 minutes before the endoscopy for sedation. The biopsy specimens were taken from four sites (the body, antrum, esophagus, and the duodenal bulb), and they were fixed in 10% formalin, paraffin-embedded sections stained with hematoxylin and eosin. Two blinded pathologists evaluated the biopsy specimens.

Visual analogue scales according to the updated Sydney scoring system on a four-point scale (0=normal/absent, 1=mild, 2=moderate and 3=marked)[18] was used for the scoring of *H. pylori* density.

Written informed consent was obtained from the parents before the procedures. The study was approved by the Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (number: 1100, date: 10.23.2018).

Statistical Analysis

Statistical analyses were performed by the IBM SPSS Statistics 22 (IBM Corp, Armonk, NY). All results are expressed as the mean ± standard deviation. The analysis was conducted using Fisher's exact test, the chi-square test and Continuity (Yates) correction. P-values of <0.05 were considered statistically significant.

RESULTS

The mean age of the patients with CD was 7.12±4.64 years (range: 6 months–17 years), and 44.5% of them were male. The mean age of the controls was 7.12±4.64 years and 50% of them were male. The characteristics of the study participants are shown in Table 1.

Significant correlation was only observed between patients with diarrhea and short stature at admission and the presence of *H. pylori* (p=0.027, p=0.025, respectively).

Endoscopic appearance was significantly different between those patients with CD and the controls both in the antrum and the corpus (p<0.001). Superficial gastritis was more common in those patients with CD than in the control group in the antrum and the corpus. Nodularity was more frequent in the control group in the antrum and the corpus than in the patient group. Comparison of the endoscopic findings between patients regarding whether they had CD or not are shown in Table 2. When the endoscopic appearance of the antrum and the corpus were compared, no significant difference was obtained in those patients with CD according to the presence of *H. pylori* (p>0.05), whereas a significant difference was observed in the histopathological findings between these patients (p<0.001). The *H. pylori*-positive patients with CD and the controls had more panmucosal gastritis than the *H. pylori*-negative ones. The lymphoid aggregates differed significantly between those patients with CD and the controls (p<0.001). No significant difference was observed between the *H. pylori*-positive and *H. pylori*-negative patients with CD according to the Marsh classification (p=0.09) and gluten free diet (GFD) (p=0.42).

There was significant difference seen in macroscopic appearance both in the antrum and the corpus, and the histopathology in the antrum between the *H. pylori*-positive patients with CD and the controls (p<0.001). Nodularity in the corpus and the antrum was low and superficial gastritis was high in the *H. pylori*-positive patients with CD. No significant difference was observed in the *H. pylori*-positive patients and the controls in terms of lymphoid aggregates in the antrum (p=0.22) (Table 3), but lymphoid aggregates were significantly higher in the corpus of patients with CD than in the controls (p=0.001).

There was no significant difference in antral appearance between the *H. pylori*-negative patients with CD and the *H. pylori*-negative controls (p>0.05), but a histopathological difference was observed between these

Table 1. The clinical characteristics of the patients and the controls

	Patients with CD (n=202)	Controls (n=209)
Age (years) mean ± SD	7.12±4.64	7.7±2.8
Male/female	0.80 (90/112)	1.00 (105/104)
Duration of disease (years), mean ± SD	8.05±3.6	
Clinical presentation, n (%)		
Short stature	96 (47.5%)	
Low weight gain	94 (46.5%)	
Diarrhea	67 (33.2%)	
Abdominal distension	38 (18.8%)	
Abdominal pain	18 (8.9%)	
Weight (<3rd percentile)	91 (45%)	
Height (<3rd percentile)	91 (45%)	
Compliance with GFD, n (%)		
Compliant	148/202 (73.3%)	
Non-compliant	36/202 (17.8%)	
EMA		
Negative	43 (22.9%)	
Positive	145 (77.1%)	
Marsh Score		
1	6 (3%)	
2	8 (4%)	
3a	51 (25.2%)	
3b	62 (30.7%)	
3c	75 (37.1%)	

CD: Celiac disease, SD: standard deviation, GFD: gluten free diet, EMA: epithelial membrane antigen, n: number.

groups (p<0.001) in both the antrum and the corpus. *H. pylori*-negative patients with CD had higher superficial gastritis in the antrum and the corpus than the *H. pylori*-negative controls. Lymphoid aggregates were significantly higher in the antrum of these patients than the controls (p=0.002) (Table 3).

In addition to nonspecific findings in the duodenum of the control group, no histopathological findings were detected except lymphocytic, plasmacytic PNL and duodenitis.

Discussion

The exact mechanism of gastrointestinal diseases such as gastritis, peptic ulceration and atrophic gastritis in patients with CD is unknown.[7] It has been proposed that *H. pylori* infection may affect the development of gluten-associated enteropathy by triggering and modulating the inflammation and immune responses in the small intestine,[7,13,14] and the pH and status of the gastric mucosa can play a key role in the digestion of gluten.[15]

Table 2. Endoscopic findings of the patients and the controls

	Patients with CD (n=202)	Controls (n=209)	p-value
Endoscopic findings			
Antrum			
Nonspecific histology	29 (14.4%)	66 (31.5%)	0.0001
Superficial gastritis	114 (56.4%)	50 (23.9%)	0.0001
Panmucosal gastritis	59 (29.2%)	93 (44.5%)	0.0001
Corpus			
Nonspecific histology	53 (26.2%)	75 (35.8%)	0.04
Superficial gastritis	104 (51.4%)	76 (36.3%)	0.002
Panmucosal gastritis	45 (22.2%)	58 (27.7%)	0.21
Macroscopic appearance			
Antrum			
Normal	147 (72.7%)	121 (57.9%)	0.001
Hyperemic	38 (18.8%)	36 (17.9%)	0.70
Nodular	17 (8.4%)	52 (24.9%)	0.0001
Corpus			
Normal	159 (78.5%)	121(57.9%)	0.0001
Hyperemic	32 (16%)	36 (17.2%)	0.79
Nodular	11 (5.5%)	52 (24.9%)	0.0001
H. pylori			
Antrum			
Positive	133 (65.8%)	135 (64.6%)	0.83
Negative	69 (34.2%)	74 (35.4%)	
Corpus			
Positive	107 (52.9%)	120 (57.4%)	0.37
Negative	95 (47.1%)	89 (42.6%)	
Lymphoid aggregates			
Positive	49 (24.2%)	29 (13.9%)	0.008
Negative	153 (75.8%)	180 (86.1%)	

p<0.05 is statistically significant.
CD: Celiac disease, n: number.

Aydogdu et al.[8] reported the possible association between CD and *H. pylori* gastritis, and stated that no effect was observed in the clinical presentation of the disease, except for abdominal distension. Luzza et al.[5] observed that recurrent abdominal pain is the only distinctive symptom between *H. pylori*-positive and *H. pylori*-negative patients and a 3-month course of GFD improved all of the symptoms in these patients whether they had *H. pylori* or not. In our study, no relationship was determined between presence of *H. pylori* and gastrointestinal symptoms in those patients with CD. In contrast with the literature, we observed that prevalence of *H. pylori* was higher in those patients with growth retardation and lower in patients with diarrhea.

Borghini et al.[9] excluded the correlation between CD and *H. pylori* infection by specific antibodies detected in gastric biopsy cultures. In the study conducted by Diamanti et al.[7], no significant difference was observed in terms of histopathology and endoscopic findings between those patients with CD and those without, but there was a higher prevalence of *H. pylori* in patients with chronic gastritis in both groups. We observed a low prevalence of nodular appearance in both the antrum and the corpus in *H. pylori*-positive patients with CD. When compared with the controls, superficial gastritis was high and panmucosal gastritis was low in patients with CD independent of their *H. pylori* status. In contrast, Luzza et al.[5] reported higher antral nodularity in both *H. pylori*-positive patients with CD and controls in comparison to *H. pylori*-negative ones, and they also stated that the prevalence of *H. pylori* did not increase in those patients with CD and that clinical and pathological signs could not be related with *H. pylori*. Similarly, Crabtree et al.[6] reported that gastritis in patients with CD is mostly related with *H. pylori,* but this was not significantly different from the normal population.

It has been stated that the prevalence of *H. pylori* was low among CD patients compared with controls, and it is estimated to be between 4% and 35%,[13-15] due to the effect of antigenicity of gliadin on the gastric acids. CD can develop at any age.[19,20] It is questionable if the presence of *H. pylori* is protective against the development of CD.[21,22] It has also been proposed that the presence of *H. pylori* can be associated with less severe villous atrophy.[21,23]

The mechanism of protection of *H. pylori* against CD is unknown. The association between *H. pylori* and a decreased the risks of allergies, atopic diseases and other inflammatory disorders has been reported,[24-26] indicating the involvement of both local and systemic regulatory T-regulatory lymphocytes in the gastric mucosa in those patients with *H. pylori*.[27,28] Lebwohl et al.[15] stated that those patients without *H. pylori* and gastric T-regulatory cells may not reduce immune responses to gluten and *H. pylori* may affect ingested gluten by modifying gastric pH or its proteases[29] and decrease its immunogenicity. Lucero et al.[30] mentioned that *H. pylori* infection rates were not different among participants whether they had CD or not, but patients with CD who had infection with *cagA*+ strains had milder histological damage, suggesting that *cagA*+ H. pylori may be protective against CD progression.

Luzza et al.[5] reported that the rate of *H. pylori* positivity was similar among children whether they were given treatment or not, whereas Ciacci et al.[13] observed that the *H. pylori* infection was significantly lower in untreated adult patients with CD than in the treated patients and the controls. Increased *H. pylori* prevalence in the treated patients can be explained by GFD-induced changes in the intestinal environment and/or the host immuno-response. In our study, no significant difference

Table 3. Comparison of endoscopic and histopatological findings between the patients and the controls

Patients with CD					controls				
	H. pylori (+)		H. pylori (-)		H. pylori (+)		H. pylori (-)		p-value
	Antrum	Corpus	Antrum	Corpus	Antrum	Corpus	Antrum	Corpus	
Normal mucosa	84 (63.3%)	77 (71.9%)	47 (68.3%)	70 (73.2%)	63 (46.7%)	60 (50%)	58 (78.4%)	61 (68.5%)	0.71
Hyperemia	30 (22.8%)	18 (17.2%)	17 (24.4%)	22 (23.2%)	25 (18.5%)	18 (15%)	11 (14.9%)	18 (20.2%)	0.54
Nodularity	19 (13.9%)	12 (10.9%)	5 (7.3%)	3 (3.6%)	47 (34.8%)	42 (35%)	5 (6.8%)	10 (11.2%)	<0.001
Nonspecific	3 (2.5%)	5 (4.7%)	25 (36.6%)	48 (50%)	7 (5.2%)	11 (9.2%)	59 (79.7%)	63 (70.8%)	0.81
Superficial gastritis	77 (58.2%)	60 (56.3%)	37 (53.7%)	44 (46.4%)	39 (28.9%)	60 (50%)	11 (14.9%)	16 (18%)	<0.001
Panmucosal gastritis	52 (39.2%)	42 (39.1%)	7 (9.8%)	3 (3.6%)	89 (65.9%)	49 (40.8%)	4 (5.4%)	10 (11.2%)	<0.001
Lymphoid aggregates	35 (26.6%)	42 (39.1%)	13 (19.5%)	7 (7.1%)	27 (20%)	24 (20%)	2 (2.7%)	5 (5.6%)	<0.001

$p<0.05$ is statistically significant.
CD: Celiac disease

was observed in *H. pylori* prevalence between those patients who were compliant with GFDs and those who were not.

CONCLUSION

In conclusion, no significant correlation was established between CD and *H. pylori* infection in our study. We observed that *H. pylori* increases the rate of gastritis in pediatric patients with CD, but this difference was not significant when compared with those children without CD. As stated in the literature in recent years, we believe that it would be more enlightening to perform immunological studies of T-regulatory cells and their associated cytokines, both in the serum and in the tissue, in those patients with HP gastritis and CD, in order to explain the etiopathogenesis.

MAIN POINTS

- The association between *H. pylori* and the natural course of CD is controversial.
- *H. pylori* increases the rate of gastritis in pediatric patients with CD.
- No significant difference was observed in the prevalence of *H. pylori* infections between those pediatric patients with CD or without.

ETHICS

Ethics Committee Approval: The study was approved by the Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (number: 1100, date: 10.23.2018).

Informed Consent: Written informed consent was obtained from the parents before the procedures.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.U., Design: N.U., Data Collection and/or Processing: Z.C., Analysis and/or Interpretation: B.Ö., Literature Search: Z.C., N.U., M.U., M.B.Ö., Writing: N.U., Critical Review: N.U., M.U.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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