Prevalence of *Helicobacter pylori* in Turkish children with celiac disease and its effect on clinical, histopathological, and laboratory parameters

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Submitted: 3 August 2018
Accepted: 8 September 2018

Arch Med Sci 2019; 15 (6): 1475–1481
DOI: https://doi.org/10.5114/aoms.2019.83699
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Abstract

Introduction: The aim of the study was to assess the prevalence of *Helicobacter pylori* (HP) in children with celiac disease (CD) and its relationship with clinical, histopathological, and laboratory parameters.
Material and methods: Two hundred and fifty-six patients with serologically and histopathologically diagnosed CD at the Pediatric Gastroenterology Department, Turkey, from January 2012 to March 2017, were included in the study, as well as 1012 patients with dyspeptic complaints. Biopsies of the duodenum and antrum were taken; the existence of HP and the histological level of damage were studied. HP (+) and HP (–) cases were compared according to age, sex, noted complaints, and clinical and laboratory features.
Results: Seventy (27.4%) CD patients and 270 (26.7%) patients with dyspeptic complaints were HP (+). The diagnostic age was higher in HP (+) cases, and diarrhea and abdominal distension were significantly higher. Although hemoglobin, ferritin, vitamin B_{12}, and transferrin saturation were lower in HP (+) cases, the differences were not statistically significant. The serum folate level in the HP (+) group was significantly lower compared to the HP (–) group.
Conclusions: The prevalence of HP was not increased in cases of CD. The CD was diagnosed later in HP (+) cases, distension and diarrhea complaints were more frequent, and folate deficiency was significant.

Key words: celiac diseases, *Helicobacter pylori*, childhood, prevalence, anemia.

Introduction

Celiac disease (CD) is a chronic autoimmune disease developed by the T helper (Th) cell-mediated immune mechanism, which is observed in individuals with a genetic predisposition and is triggered by gluten in products such as wheat, barley, and rye. The frequency of CD varies depending on the geographical region; it is most frequently observed in countries/regions such as Turkey, Western Europe, Northern America, and Australia, where wheat has a significant role in nutrition. Environmental, immunological, and genetic factors act together in the pathogenesis of CD [1, 2]. Celiac disease has a wide range of symptoms. Some cases can be asymptomatic whereas others may lead to death.

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The prevalence of celiac disease varies between 1 : 100 and 1 : 200 in Europe [3–5], whereas it is 0.47% in Turkey [6]. In the USA, the prevalence of CD is rising and has quadrupled in the last 50 years [7, 8].

Various symptoms and findings can be observed, including gastrointestinal symptoms, such as dyspepsia, abdominal distension, and diarrhea, as well as findings such as osteoporosis due to insufficient absorption of micronutrients, and anemia. Classical CD is related to intraepithelial lymphocyte detriment, resulting in damage to the small intestinal mucosa [8, 9].

Helicobacter pylori (HP) is a frequently observed antibiotic-resistant bacterial infection. The HP infection affects almost half of the population worldwide. While its prevalence can be up to 90% in developing countries, its prevalence is < 40% in developed countries [10]. The HP is mostly found in the stomach and causes B cell lymphoma, gastric carcinoma, peptic ulcers, and gastritis. The worldwide prevalence of HP has been decreasing in recent years, which coincides with the increased prevalence of CD in the USA [11]. The relationship between HP infection and CD is not clear; the literature contains many contradictory results.

The HP infection can influence the development and evolution of gluten-related enteropathy by regulating the inflammatory and immune responses in the small intestine [12, 13]. However, while some studies state that there is no relationship between these two diseases, others have reported that HP can provide protection against CD [14].

The etiology, prognosis, and significance of gastric involvement in CD are unknown [15]. In previous studies, HP was reported to be related to gastritis and anemia in people with CD [16, 17]. We aimed to determine the prevalence of HP infection in subjects with CD. We also investigated the possible association between HP infection, degree of histological damage, and the role of HP infection in the clinical, laboratory, and histopathological presentation in children with CD.

Material and methods

The study included 256 patients serologically and histopathologically diagnosed with CD and aged between 1 and 18 years old who presented to the Pediatric Gastroenterology Department, Medical Faculty, Çukurova University, between January 2012 and March 2017. In addition, to assess the HP prevalence during the period of the study, 1012 subjects who underwent an upper gastrointestinal endoscopy but did not have CD were included in the study. The exclusion criteria included the previous use of antibiotics for HP eradication, or proton-pump inhibitors and histamine (H2) receptor blockers within 3 weeks before the endoscopy, as these would affect the presence of HP. The demographic, clinic, laboratory, serological, and histopathological findings were derived from the patient files during the diagnosis. After 8 h of fasting, midazolam 0.1 mg/kg and propofol 1 mg/kg were administered for sedation before performing the endoscopy with a Pentax EG-2730K gastroscope (Pentax, Tokyo, Japan).

During the upper gastrointestinal endoscopy, biopsies from the duodenum, antrum, and corpus were taken according to the protocols reported in previous studies [18]. The presence of HP was investigated via histological staining with hematoxylin-eosin and Giemsa. The degree of histological stomach damage and duodenal biopsies of HP (+) and HP (–) CD patients were compared. The diagnosis of CD was based on the characteristic histological finding of increased intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia classified according to the standard classification proposed by Marsh. The histopathological evaluation was conducted according to the Marsh classification [2, 19]. The assessment of gastritis was performed according to the modified Sydney System [20].

HP (+) and HP (–) cases were compared according to age, sex, applied complaints, and the clinical and laboratory features (hemogram, total protein, albumin, folic acid, vitamin B_{12}, serum iron, ferritin, serum iron-binding capacity, thyroid function tests). Anemia was defined as a hemoglobin concentration < 11.5 g/dl in those aged 2–9 years, and < 12.5 g/dl in those aged 10–18 years. Iron deficiency was defined as a ferritin level < 10 ng/dl. Iron deficiency anemia (IDA) was defined as the presence of low serum iron levels (normal range: 22–184 µg/dl), high iron binding capacity (normal range: 250–400 µg/dl) and iron deficiency [21]. Families and patients were informed about the endoscopy, colonoscopy, and enteroscopy procedures, and written informed consent was obtained. The Cukurova University School of Medicine local ethics committee approved this retrospective study.

Statistical analysis

All analyses were performed using the IBM SPSS Statistics Version 20.0 statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as the mean and standard deviation, or as the median and minimum-maximum where appropriate. The χ^2 test was used to compare categorical variables between the groups. For comparison of continuous variables between two groups, Student's *t*-test was used. The statistical level of significance for all tests was considered to be 0.05.

Results

HP prevalence, demographic, endoscopic and clinical findings of non-celiac cases

During the study process, upper gastrointestinal system endoscopy was performed in 1012 patients who had gastrointestinal complaints and who did not have CD. The endoscopic findings of these patients were antral gastritis (20%), duodenogastric reflux and antral gastritis (8%), duodenogastric reflux and pangastritis (10%), peptic ulcer (2.2%), esophagitis (10%), eosinophilic esophagitis (0.5%), pangastritis (10%), duodenitis (10%), bulbitis (12%), low esophageal sphincter incompetency (6%), esophageal ulcer (1.5%), esophagitis and antral gastritis (4%), and normal (6%). HP (+) was determined in 270 (26.7%) of these patients. The mean age of the patients who did not have CD and who were HP (+) was 14 ±3.1 years; and the mean age of the patients who did not have CD and who were HP (–) was 8 ±3.2 years. This rate was higher at a significant level ($p < 0.05$). No statistically significant differences were detected between the patients who did not have CD and who were HP (+) and those who did not have CD and who were HP (–) in terms of gender.

HP prevalence rate and demographic and clinical findings of HP (+) and HP (–) patients with celiac disease

Twenty-seven (27.4%) of the 256 patients serologically and histopathologically diagnosed with CD were found to be HP (+). The mean age of the patients who had CD and who were HP (+) was 11 ±3.8 years, and the mean age of the patients who had CD and who were HP (–) was 7.6 ±4.2 years. This rate was high at a significant level ($p < 0.05$). No statistically significant differences were detected between the patients who had CD and who were HP (+) and those who had CD and who were HP (–) in terms of gender.

In HP (+) patients with CD, the most frequently observed findings and symptoms were growth failure (60%), abdominal pain (40%), and diarrhea (39%). However, in HP (–) patients with CD, growth failure (67%), abdominal pain (38%), and asthenia (26%) were frequently observed. Complaints of diarrhea and abdominal distension were significantly higher in HP (+) CD patients than HP (–) CD patients ($p < 0.05$), whereas complaints of constipation and asthenia were significantly higher in HP (–) CD patients ($p < 0.005$) (Table I).

Duodenal and gastric histopathological findings in HP (+) and HP (–) patients with celiac disease

In the histopathologic examination of the small intestine of HP (+) CD patients, 16 (23%) cases were classified as Marsh 3A, 39 (56%) cases were Marsh 3B, and 15 (21%) cases Marsh 3C. The finding of Marsh 3A was significantly higher in the HP (–) group ($p < 0.05$). Among the HP (–) cases, 61 (33%) were Marsh 3A, 72 (39%) were 3B, and 53 (29%) were 3C (Table II).

In stomach biopsies from HP (+) CD patients, the activity and chronicity were significantly higher than in the HP (–) CD patients. Atrophy was detected in two HP (+) cases and intestinal metaplasia was detected in 3 cases (Table III).

Table I. Demographic and clinical comparison of HP (+) and HP (–) patients with celiac disease

Parameter	HP (+) celiac disease (n = 70)	HP (–) celiac disease (n = 186)	*P*-value
Age	11 ±3.8	7.6 ±4.2	0.005
Male	36 (51%)	83 (47%)	0.399
Female	34 (49%)	103 (54%)	0.201
Growth failure	48 (69%)	124 (67%)	0.881
Inappetence	12 (17%)	28 (15%)	0.701
Asthenia	21 (10%)	19 (30%)	0.005
Nausea	4 (6%)	9 (5%)	0.755
Vomiting	3 (4%)	18 (10%)	0.206
Abdominal pain	28 (40%)	70 (38%)	0.774
Distension	21 (30%)	26 (14%)	0.006
Diarrhea	27 (39%)	36 (19%)	0.002
Constipation	4 (6%)	48 (26%)	0.002

HP – Helicobacter pylori.

Table II. Duodenal histopathological findings in of HP (+) and HP (–) patients with celiac disease

Marsh	HP (+) celiac disease (n = 70)	HP (–) celiac disease (n = 186)	P-value
3A	16 (23%)	61 (33%)	0.04
3B	39 (56%)	72 (39%)	0.05
3C	15 (21%)	53 (29%)	0.78

HP – Helicobacter pylori.

Table III. Gastric histopathological findings in of HP (+) and HP (–) patients with celiac disease

Parameter	HP (+) celiac disease (n = 70)	HP (–) celiac disease (n = 186)	P-value
Activity:			
Mild	29 (41%)	57 (31%)	0.001
Medium	21 (30%)	7 (4%)	0.001
Severe			
Chronicity:			
Mild	42 (60%)	99 (53%)	0.001
Medium	26 (37%)	9 (5%)	0.001
Severe	1	–	
Atrophy	2	–	
Intestinal metaplasia	3	–	

Laboratory parameters in HP (+) and HP (–) patients with celiac disease

Anemia was detected in 37 (53%) of HP (+) and 91 (49%) of HP (–) cases. There were no significant differences between the two groups with regards to white blood cell count (WBC), hemoglobin levels, red blood cell distribution width (RDW), median corpuscular volume (MCV), thrombocyte, total protein, albumin, folic acid, vitamin B_{12}, serum iron, ferritin, serum iron binding capacity, or the thyroid function test. The serum folate level in the HP (+) group was significantly lower than in the HP (–) group ($p < 0.05$) (Table IV). Additionally, no significant differences in the standard deviation (SD) weight and height scores were detected between the groups.

Discussion

Although the majority of the people who were infected with HP were asymptomatic, HP is reported to be the main cause of chronic gastritis as well as peptic ulcers, gastric adenocarcinoma, and primary mucosa associated lymphoid tissue (MALT) lymphoma, which are also major complications of chronic gastritis. There are numerous studies on the possible role of this bacterium in the etiology in both gastrointestinal and extra-gastrointestinal situations. These studies have concluded that while HP infection can cause some diseases, it can also protect against others [22]. For example, it was reported that HP infection decreases the risk of allergic reactions, atopic diseases, autoimmune thyroid disease, autoimmune gastritis and other inflammatory situations [23–25].

Although a relationship between CD and HP has been observed in some studies, the results were contradictory due to the differing prevalence of HP in different societies [26]. In the USA, the prevalence of CD is increasing, whereas the prevalence of HP is simultaneously decreasing [11]. Furthermore, Lebwohl *et al.* [27] reported that the risk of CD development was decreased with HP infection; the presence of HP infection was 4.4% in cases with CD and 8.8% in cases without CD. In contrast, Konturek *et al.* [28] reported a HP infection prevalence of 26.4% in CD cases, but only 20% in controls; therefore, the prevalence of HP infection was increased in CD cases. However, CagA positive HP strains were lower in CD cases compared to non-CD cases. Therefore, they stated that virulent strains may be protective against CD [28].

In previous studies including adults, the prevalence of HP infection in CD and controls has been reported as 29.3% and 30% [29], 82% and 91.9% [30], 12.5% and 30% ($p < 0.005$) [31], and 36% and 41%, respectively [32]. On the other hand, studies including children have reported the prevalence of HP infection in CD and controls as 18.5% and 17.3% [33], and 21.8% and 23.8%, respectively [14].

Table IV. Comparison of laboratory parameter in of HP (+) and HP (–) patients with celiac disease

Parameter	HP (+) celiac disease (*n* = 70)	HP (–) celiac disease (*n* = 186)	*P*-value
WBC [× 10^3µ/l]	8109 ±2492	8466 ±2722	0.321
Hemoglobin [g/dl]	11.8 ±1.8	11.5 ±1.68	0.342
MCV [fl]	76.4 ±8	75.3 ±7.7	0.320
Platelet count [× 10^3µ/l]	331900 ±101792	352876 ±96625	0.139
RDW (%)	16.1 ±3.6	15.7 ±3.2	0.458
Iron [µg/dl]	54.2 ±34	59.4 ±37.6	0.450
TIBC [µg/dl]	382.7 ±63.7	366.1 ±70.5	0.198
Ferritin [ng/ml]	11.6 ±9.6	14.5 ±12.8	0.237
Vitamin B_{12} [pg/ml]	285.4 ±153	325 ±195	0.280
Folic acid [ng/ml]	7.6 ±4	10.5 ±6.6	**0.004**
Total protein [g/dl]	6.7 ±0.6	6.6 ±0.6	0.701
Serum albumin [g/dl]	4.1 ±0.39	4 ±0.47	0.601
tTGA [U/ml]	301 ±229	277 ±201	0.450
EMA [U/ml]	234 ±138	237 ±153	0.409
TSH [mIU/l]	2 ±1.1	2.5 ±2.3	0.200
fT_4 [mIU/l]	0.8 ±0.2	0.8 ±0.24	0.303

WBC – white blood cells, MCV – median corpuscular volume, RDW – red cell distribution width, TIBC – total iron binding capacity, tTGA – tissue transglutaminase antibody, EMA – anti-endomysium antibodies, TSH – thyroid-stimulating hormone, fT_4 – free thyroxine. Significant values shown in bold.

Turkey is considered to be an interesting region as it may receive influences from Asian and Western countries showing high and low *H. pylori* prevalence rates, respectively [34]. The HP prevalence rates were reported to be between 23.6% and 75.8% in the eastern part of Turkey, and 30.9% in the southern part of Turkey [35–37]. In another study we conducted in our center between 2013 and 2014 with 2–18-year-old children, we determined the HP prevalence rate as 30.7% [38].The prevalence rates were higher compared to Europe (18%), near to those reported for Asia (35%) [39]. We found the HP prevalence to be similar in patients with and without CD (27.3% and 26.7%, respectively).

The variety of results observed in these studies may be caused by different diagnostic techniques, age, sex, socio-economic differences, geography, and the population that participated in the studies. Therefore, when choosing a control group, it is important to consider these variables. In our study, all cases of gastrointestinal system complaints were from a similar age group and the same geographical location.

In the period when we conducted the study, Turkey was included in the "Upper Middle Income" group in economic terms according to the World Bank data. Our values were higher than those reported for Europe and close to or lower than those reported for Asia and other Eastern countries.

Previous studies have suggested the "hygiene hypothesis" as an explanation for the phenomenon of HP infection protecting against CD autoimmunity [27, 40]. It was stated that potential complex interactions between untreated CD and HP infection can affect the Th1/Th2 immune balance in the stomach mucosa. Local and systematic damage of the gastric mucosa in HP (+) patients by affecting T regulatory lymphocytes were also considered [41].

The results from studies on the effect of CD on stomach and duodenal histopathology are also controversial. Aydogdu *et al.* [14] reported very mild duodenal lesions in patients with HP gastritis. Similarly, Siamondi *et al.* [32] also detected a slight correlation between duodenal histological findings and HP prevalence. Kupcinskas and Malfeltheiner [22] reported that the presence of HP infection was observed more frequently in CD patients with a slight change in their histopathology. There are also some studies that claim the opposite argument; for example, Rostami-Nejad *et al.* [30] reported that there is no relationship between histopathological damage and HP infection in CD cases. Furthermore, Lasa *et al.* [31] reported that HP infection does not affect the histological

severity of CD. Similarly, in our study, we did not detect any effect of HP positivity on duodenal histopathological findings. In the gastric histopathological examination of HP (+) CD patients, we observed atrophy in two cases and intestinal metaplasia in three cases. Moderate and severe activity and chronicity were significantly higher in HP (+) CD cases compared to HP (–) CD cases, although we did not detect gastric metaplasia. Aydogdu *et al.* [14] demonstrated accompanying gastric metaplasia in HP (+) cases and stated that it was more frequent compared to HP (–) cases.

It has been reported that HP infection causes iron deficiency anemia by various mechanisms, such as occult bleeding due to chronic erosive gastritis; decreased iron absorption due to chronic gastritis; hypochlorhydria; achlorhydria, and bacterial use of iron [42]. Cuoco *et al.* [16] stated that iron deficiency anemia development in CD patients was related to a decreased iron intake, decreased iron absorption, and nutrition. In previous epidemiologic studies, a relationship between HP infection and iron deficiency was reported; however, the mechanism of this relationship is not fully understood [16, 43, 44]. Couco *et al.* [16] suggested treatment of HP infection in CD with a gluten-free diet. Aydogdu *et al.* [14] did not find any statistically significant difference between HP (+) and HP (–) CD cases with regards to levels of hemoglobin, MCV, thrombocyte, ferritin, albumin, vitamin B_{12}, folic acid, transferrin saturation, iron deficiency anemia, or anemia. Simondi *et al.* [32] and Demir *et al.* [44] did not find any relationship between iron deficiency anemia and HP infection in CD. In our study, statistically significant differences in serum hemoglobin concentration, serum iron, ferritin, and increased serum iron-binding capacity were not detected between the two groups. However, folic acid level was found to be significantly lower in cases with HP infection. In this study, HP infection was not found to have any effect on the development of iron deficiency in children with CD.

In our study, while diarrhea and abdominal distension were observed in CD patients with HP infection, constipation was observed in HP (–) CD cases. It was also observed that all complaints were resolved by a gluten-free diet.

One of the limitations of our study was not being able to investigate HP in a healthy group. We did not consider it to be ethical to apply such an invasive and risky process as endoscopy to healthy individuals. However, we had to include patients who were diagnosed with an indication to receive endoscopy and who had complaints about the gastrointestinal system in the control group.

In conclusion, the relationship between CD and HP infection and its effect on clinical and laboratory parameters have not yet been demonstrated clearly in the literature. In our study, the HP prevalence in CD patients is similar to that of the population that does not have CD, and is not higher at a significant level. We did not find a protective relationship between *H. pylori* and celiac disease. We observed that CD cases with HP infection in Turkish children were diagnosed later and presented with frequent complaints of distension and diarrhea, with a significantly lower level of folate deficiency. It should be considered that gastrointestinal findings in CD patients can vary greatly with differing ages. We believe that in HP (+) cases, particularly in older children, physicians should also consider CD in the presence of distension and diarrhea complaints.

Conflict of interest

The authors declare no conflict of interest.

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