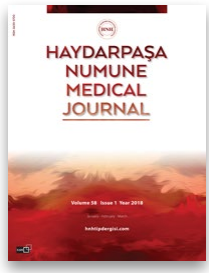
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ORIGINAL ARTICLE

Is There any Relation between the Presence of *Helicobacter Pylori* Infection and Duodenogastric Reflux in Children?

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Abstract

Introduction: Although it is a bile-sensitive microorganism in vitro, *Helicobacter pylori* (Hp) has been detected in human bile and gallbladder tissue. Recently, it is reported that bile acids eliminate Hp after gastric surgery. However, the data about the relationship between Hp and bile acids in subjects without surgery are limited. We aimed to evaluate the clinical features and Hp gastritis rate among patients with and without reflux of gastric bile acid.

Methods: Patient data were collected through reviewing medical records of 1–18-years old children who underwent gastroscopy during the study period. The rapid urease test (RUT) result, the presence of gastric or bulbar erosion/ulcer, and duodenogastric reflux (DGR) were obtained from gastroscopy reports. Histologic changes of alkaline gastritis and other types of gastritis were noted. Hp infection was accepted as "present" if both RUT and histopathological findings confirm the Hp presence.

Results: Among 754 diagnostic esophago-gastro-duodenoscopy (EGD), 521 subjects were eligible. Bile was visible at the stomach in 114 children (mean age: 11.29±3.90 years, 76.3% girls). The remaining 407 children without bile in the stomach were served as controls (mean age: 9.09±4.53 years, 52.1% girls). Girl gender was a risk factor for bile in the stomach during EGD (aOdds Ratio [aOR]: 1.33, 95% confidence interval [CI]: 1.09–1.77, $p<0.05$). Hp was present in 35 (30.7%) subjects in the study group and 210 (51.6%) controls (OR: 1.68, 95% CI: 1.25–2.24, $p<0.05$). Foveolar hyperplasia was present in 98 (86.0%) cases in the study group and 2 (0.5%) controls. Alkaline gastritis was correlated with bile in the stomach (r^2: 0.89, $p<0.01$), older age (r^2: 0.18, $p<0.01$), and girl gender (r^2: 0.21, $p<0.01$).

Discussion and Conclusion: The rate of Hp infection was lower in patients with DGR compared to controls. Furthermore, DGR was significantly more frequent in girls and grown-up children. A high percentage of patients with bile reflux had alkaline gastritis.

Keywords: Alkaline gastritis; bile acids; children; duodenogastric reflux; *Helicobacter pylori*.

Duodenogastric reflux (DGR) results from excessive reflux of bile and duodenal contents into the stomach. It is one of the primary factors involved in the pathophysiological processes leading to gastric mucosal damage in chronic gastritis patients[1,2]. DGR can develop after cholecystectomy, pyloroplasty, gastric surgery, and primarily[1].

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Short-term DGR might occur physiologically, causing a few symptoms such as temporary epigastric pain and nausea postprandially or during prolonged fasting. Pathological DGR lasts for an extended time and excessive bile reflux might cause bile reflux gastritis (BRG)[2].

Helicobacter pylori (Hp) infection is the most prevalent gastric bacterial infection. It colonizes the gastric mucosa often during early childhood and might persist throughout life. Hp is highly associated with chronic gastritis, peptic ulcers, gastric mucosal atrophy, metaplasia, dysplasia, lymphoma, and gastric adenocarcinoma[3]. Despite the fact that it is a bile-sensitive microorganism in vitro, Hp has previously been detected paradoxically in human bile and gallbladder tissue[4]. It has been postulated that gastric acid secretion would neutralize the alkaline pH bile acid; thereby, Hp resists and colonizes the gastric mucosa[5]. Recently, it is reported that bile acids eliminate Hp after gastric surgery[6]. However, it has been suggested that gastric bile acids may suppress the initial stages of Hp infection in subjects without gastric surgery[7]. The relationship between DGR of bile and gastric colonization of Hp or Hp gastritis has given conflicting results. We aimed to evaluate the clinical features and Hp gastritis rate among patients with and without reflux of gastric bile acid.

Materials and Methods

In this study, 1-18-year-old children who underwent a diagnostic esophago-gastro-duodenoscopy (EGD) from January 2018 to December 2020 were included in the study. Patient data were retrieved through reviewing medical records. The patients' demographic features, complaints, medication history, EGD, and histopathological findings were analyzed retrospectively.

The rapid urease test (RUT) result, the presence of gastric or bulbar erosion/ulcer, and the presence of DGR were obtained from EGD reports. DGR was diagnosed if bile was visible in the stomach during gastroscopy, similar to the previous studies[6,7]. Gastritis subtypes (chronic active gastritis, chronic inactive gastritis, alkaline gastritis, or chronic lymphocytic gastritis) and the presence of Hp infection were classified from histopathological reports in accordance with Sydney scoring system. Hp infection is accepted as "present" if both RUT and histopathological findings confirm the Hp presence. Histologic changes of alkaline gastritis were also noted.

Children with incomplete medical records, emergent EGD, previous Hp eradication, receiving acid-suppressive, or antibiotic therapy at least 4 weeks before EGD were the exclusion criteria. Moreover, patients with other chronic disease such as Type 1 diabetes mellitus, inflammatory bowel diseases, renal, metabolic, liver, or heart diseases were excluded from the study. The study protocol was approved by the Local Ethics Committee (March 17, 2021, decision no: 76).

Data were analyzed using SPSS software (IBM SPSS version 20, IBM Corp., New York, USA). Continuous variables are presented as mean±standard deviation, and categorical variables are presented as numbers or percentages. The Shapiro–Wilk test tested the normality of data. The Student's t-test was used to compare means. Pearson Chi-square was used to compare categorical variables, and odds ratio (OR) and 95% confidence intervals (CI) for independence were specified. When the outcome is a binary variable, categorical variables were analyzed by logistic regression with adjustment for age and gender, then adjusted aOR and 95% CI for independence were specified. For metric variables, Pearson's correlation coefficients were computed. Calculated $p<0.05$ indicated statistical significance.

Results

Among 754 diagnostic EGD between January 2018 and December 2020, 521 subjects were eligible for the study. The excluded subjects were: 32 with inadequate data, 74 with celiac disease, 69 cases with the previous Hp eradication, 39 cases with recent antibiotic or anti-acid drug use, and 19 cases with a chronic disease.

Bile was visible at the stomach in 114 children (mean age: 11.29±3.90 years, 76.3% girls). The remaining 407 children without visible bile in the stomach were served as controls (mean age: 9.09±4.53 years, 52.1% girls). Group characteristics are summarized in Table 1. Patient complaints at referral were similar ($p>0.05$). There were significant differences among the groups regarding age and gender ($p<0.05$). Girl gender was a risk factor for visible bile in the stomach during EGD (OR: 2.02, 95% CI: 1.43–2.85, $p<0.05$). After adjustment for age, being a girl was still a risk factor (aOR: 1.33, 95% CI: 1.09–1.77, $p<0.05$). Hp was present in 245 (47.0%) cases in total. However, 35 (30.7%) subjects in the study group and 210 (51.6%) subjects in the control group were infected by Hp (OR: 1.68, 95% CI: 1.25–2.24, $p<0.05$).

Foveolar hyperplasia and other histologic findings of BRG were present in 98 (86.0%) cases in the study group and 2 (0.5%) cases in the control group. Alkaline bile gastri-

Table 1. Demographic features of the patients

	Study group (n=114)	Control group (n=407)	p
Mean age±SD (year)	11.29±3.90	9.09±4.53	<0.05
Gender (girl, %)	76.3	52.1	<0.05
Complaints (n,%)[a]			
Recurrent abdominal pain	77 (67.5)	244 (59.9)	>0.05
Dyspepsia	32 (28.1)	142 (34.8)	>0.05
Nausea/Vomiting	35 (30.7)	130 (31.9)	>0.05
Losing/Not gaining weight	45 (39.5)	118 (29.0)	>0.05
Short stature	37 (32.4)	130 (31.9)	>0.05
Others[b]	61 (53.5)	228 (56.1)	>0.05
Helicobacter Pylori (n,%)	35 (30.7)	210 (51.6)	<0.05
Alkalen gastritis (n,%)	98 (86.0)	2 (0.5)	<0.05

[a]Some patients presented with more than one complaint; [b]Other complaints: Abdominal bloating and flatulence, diarrhea, constipation, dysphagia/odynophagia.

tis was correlated with visible bile in the stomach (r^2:0.89, p<0.01), older age (r^2:0.18, p<0.01), and girl gender (r^2: 0.21, p<0.01).

Discussion

In this study, we demonstrated that the Hp infection rate was lower in patients with DGR than those without DGR. Furthermore, DGR was significantly higher in girls and teenagers. A high percentage of patients with bile reflux had alkaline gastritis. There are conflicting results on the relationship between Hp and DGR. It was reported that bile reaching the stomach with DGR inhibits Hp colonization by disrupting the stomach mucosal barrier and forming an alkaline medium[8,9]. Thus, the rate of Hp infection was lower in these patients.

On the contrary, some studies reported no relation in terms of Hp presence, whether the patient had DGR or not[10,11]. There is little information about this subject in pediatric patients. Recently, Ağin et al.[12] reported that the stomach's bile presence did not affect the Hp colonization in children. However, we determined that the Hp infection rate was lower in pediatric patients with DGR in this study. These results are consistent with the notion that bile acid may inhibit Hp infection in the stomach. It is suggested that there are some factors such as the virulence factors of Hp, the pH of the gastric content, and the structure and density of bile acids affecting the presence and severity of Hp infection in patients with DGR[13-15]. Such factors should be elucidated by future mechanistic research in patients with DGR to explain these discrepancies.

The reflux of duodenal contents into the stomach is prevalent in adults, especially after gastrointestinal surgery and cholecystectomy; however, it is less common in patients without previous surgery. DGR is more frequent in early adulthood (notably in 21–30 years of age) and older population (notably over 71 years of age)[16]. In children, it was shown that DGR was frequently found in young adolescents[12]. Consistent with this data, the average age of the patients with DGR was significantly higher than that of the patients without DGR in our study. There is little information about the relation between DGR and gender, and higher DGR rates in female patients were reported in adult studies[17]. The ovulatory cycle might have a role in the increased rates of DGR in females since it was shown that serum bile acid concentrations fluctuate during the cycle[18]. In pediatric patients, no significant relationship between DGR and gender was previously reported[12]. Therefore, we found that the girls had significantly higher rates of DGR than boys. No symptoms were found to be characteristic enough to identify the patients with DGR, and there was no statistical difference between the two groups according to symptoms in our study.

The characteristic histological features of BRG, including antral foveolar hyperplasia, vascular congestion, edema, smooth muscle fibers in the lamina propria, and a paucity of inflammatory cells, were identified in adults. Nevertheless, the histological findings of gastric mucosa in children with BRG remain unclear[1,19]. Zhang et al.[2] reported that foveolar hyperplasia is associated with the degree of bile reflux and may serve as the characteristic histological change of primary BRG in children. In accordance with these findings, foveolar hyperplasia and other histologic findings of BRG were present in 86% of our patients with DGR. The gold standard to determine the DGR in children is

24-h ambulatory bile monitoring in the stomach. However, this procedure is more invasive, impractical, and inaccessible for many centers. Foveolar hyperplasia is the cardinal histologic feature of reactive/alkaline gastropathy. The high foveolar hyperplasia rate correlated with DGR in our study reflects that our DGR definition is feasible.

Hp infection was infrequent in patients with DGR in our study. This data support that the idea of Hp colonization may be inhibited by gastric bile acid content. Further studies are required to increase our understanding of the association between Hp infection and bile acid reflux in patients with gastritis.

Ethics Committee Approval: The study protocol was approved by the local Ethics Committee (17.03.2021, decision no:76). This study was conducted in accordance with the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: N.A.B.; Design: B.V., N.A.B.; Data Collection or Processing: B.V., N.A.B.; Analysis or interpretation: N.A.B.; Literature search: B.V.; Writing: B.V., N.A.B.

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