ORIGINAL ARTICLE

Relationship between *Helicobacter pylori* Infection and Gastrointestinal Symptoms in Children

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ABSTRACT

Objective: *To examine the relationship between Helicobacter pylori* (H. pylori) *infection and gastrointestinal symptoms, and the efficacy of eradication treatment.*

Methods: *A retrospective chart review was carried for children (5–18 years old), who underwent a ^{14}C-urea breath test (^{14}C-UBT) for* H. pylori *infection. Pre- and post-treatment ^{14}C-UBT results, gastrointestinal symptoms,* H. pylori *eradication protocol and treatment consistency were noted.*

Results: *At presentation, out of 537 patients (65.2% girls), 43.9% had ^{14}C-UBT positivity. The frequency of heartburn, acid regurgitation and halitosis (*$p = 0.001$, $p = 0.006$ *and* $p = 0.03$, *respectively) were significantly high in the ^{14}C-UBT (+) patients; the frequency of epigastric pain (*$p < 0.0001$*) was significantly high in the ^{14}C-UBT (–) patients at presentation. The ^{14}C-UBT (+) patients were treated with amoxicillin + lansoprazole + clarithromycin (66.1%)/ metranidazole (33.9%). After the eradication treatment, control ^{14}C-UBT was negative in 62.5% of patients treated with metranidazole compared with 47.4% of patients treated with clarithromycin protocol (*$p = 0.03$*). After the eradication treatment, the frequency of gastrointestinal symptoms (except the feeling of hunger) were significantly decreased regardless of treatment success (*$p < 0.0001$*). The frequency of total gastrointestinal symptoms (*$p < 0.0001$*), epigastric pain (*$p < 0.0001$*), epigastric burning (*$p = 0.003$*), heartburn (*$p = 0.002$*), acid regurgitation (*$p = 0.006$*), nausea (*$p = 0.001$*), halitosis (*$p = 0.02$*) and early satiety (*$p = 0.02$*) were significantly reduced in patients with control ^{14}C-UBT (–).*

Conclusion: H. pylori *eradication, or the attempt to eliminate* H. pylori*, reduces gastrointestinal symptoms in* H. pylori*-infected children.*

Keywords: Children, dyspepsia, *Helicobacter pylori*, treatment

INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common bacterial pathogens in humans and is acquired mainly during childhood. The prevalence of *H. pylori* infection is still common in developing countries. It can persist for a life time, and chronic infection is nearly always accompanied by chronic active gastritis. The *H. pylori* infection is usually asymptomatic particularly in children, however, may cause serious diseases, such as peptic ulcer disease, non-cardiac gastric adenocarcinomas and the gastric mucosa-associated lymphoid tissue lymphomas, especially in adults (1, 2). There have been conflicting reports on the relationship between *H. pylori* infection and gastrointestinal symptoms in children and

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adults. The resolution of dyspeptic symptoms after a successful *H. pylori* eradication remains controversial. Also, relation of healing of mucosa after the eradication or suppression of acid-related symptoms by proton pump inhibitors (PPIs) is debatable (2–11). We aimed to examine the relationship between gastrointestinal symptoms and *H. pylori* infection at presentation and after eradication treatment.

SUBJECTS AND METHODS

A retrospective chart review was carried out in 1850 patients who underwent a ^{14}C-urea breath test (^{14}C-UBT) for the detection of *H. pylori* infection. These patients were either primarily admitted or referred to our paediatric gastroenterology outpatient clinic after ^{14}C-UBT performed between January 2011 and January 2013. Age, gender, symptomatology and ^{14}C-UBT results at diagnosis were noted by the same observer. The records of the ^{14}C-UBT-positive patients were reviewed for the given randomized empirical treatment protocol, treatment consistency, symptomatology and post-treatment ^{14}C-UBT results by the same observer. Epigastric pain, epigastric burning, heartburn, acid regurgitation, nausea, vomiting, recurrent abdominal pain (RAP), early satiety, halitosis and a frequent feeling of hunger were considered in the symptomatology. Localized pain sensation in the epigastric region was considered as epigastric pain. Localized burning sensation in the epigastric region, not radiating up towards the throat was considered as epigastric burning. If the burning sensation was in the chest, radiated up towards the throat, it was considered heartburn.

A sudden regurgitation of acid gastric content was considered as an acid regurgitation. Inability to finish a normal meal was considered as early satiety (12). Halitosis was determined if patients complained of an unpleasant or offensive odour emanating from the oral cavity (6). Recurrent abdominal pain was defined if abdominal pain was present for at least three months, with at least three episodes, severe enough to affect child's activity (13). The 'improvement' of a symptom was defined, if only there was a complete resolution of the symptom after the eradication treatment. The ^{14}C-UBT was performed with Heliprobe® system (Kibion, Upsala, Sweden).

The study was approved by the Ethics Committee of the Turkish Republic Health Ministry, Ankara Child Health Diseases, Haematology Oncology Training and Research Hospital (2014/023 protocol number), Ankara, Turkey. Of the 1850 patient records, 537 patients (350 girls, 65.2%) met the following criteria for inclusion in the study: (a) 5–18 years of age; (b) if at least one of the above gastrointestinal symptoms was present for at least two months; (c) not treated with antimicrobial drugs or acid-suppressive drugs for at least one month prior to the ^{14}C-UBT; (d) naïve for *H. pylori* eradication treatment; (e) if treatment protocol consisted of lansoprazole (1–2 mg/kg per day, maximum: 2 × 30 mg/day) + amoxicillin (50 mg/kg per day, maximum: 2 g/day) + metranidazole (15 mg/kg per day, maximum: 1 g/day) or clarithromycin (15–20 mg/kg per day, maximum: 1 g/day) for 14 days, twice daily; (f) if the symptomatology was noted after treatment; (g) if the control ^{14}C-UBT was performed at least one month after completing the eradication treatment. Children were excluded from the study if: (a) they had a previously known peptic ulcer disease, or no gastrointestinal complaints at the presentation; (b) the treatment protocol did not include the drugs above; (c) the eradication treatment was discontinued or improperly used; (d) after the eradication treatment, a control ^{14}C-UBT was not performed; (e) the control ^{14}C-UBT was performed less than one month or more than two months after completing the eradication treatment.

Statistical analyses

Statistical analyses were performed using SPSS software (ver. 17.0, SPSS. Inc., Chicago, IL, USA). The results are presented as means ± SDs with descriptive statistics. The Student's unpaired *t*-test was used as appropriate. When the variances were unequal or the distributions not normal, the Mann–Whitney *U*-test was used. The significance level was set at $p < 0.05$.

RESULTS

Mean age of 537 patients (65.2% girls), who underwent the ^{14}C-UBT, was 11.6 ± 3.3 (range: 5–18) years old. Among 537 patients, 236 (43.9%) were ^{14}C-UBT (+) at the presentation. There were 159 (67.4%) girls among the ^{14}C-UBT (+) patients and 191 (63.5%) girls among the ^{14}C-UBT (–) patients. There was no gender difference between ^{14}C-UBT (+) and ^{14}C-UBT (–) patients at the presentation ($p > 0.05$). The ^{14}C-UBT (+) patients (12 ± 3.3 [range: 5–17.5] years) were older than the ^{14}C-UBT (–) patients (11.4 ± 3.4 [range: 5–18] years) at the presentation ($p = 0.03$).

In Table 1, the gastrointestinal symptoms of patients are given based on the ^{14}CUBT results at the presentation. Epigastric pain were more frequently observed in the ^{14}C-UBT (–) patients as compared with the ^{14}C-UBT (+) patients ($p < 0.0001$). Heartburn, acid regurgitation

and halitosis were more frequently observed in the ^{14}C-UBT (+) patients as compared with the ^{14}C-UBT (–) patients ($p = 0.001$, $p = 0.006$, $p = 0.03$, respectively). Nausea, vomiting, epigastric burning, early satiety, RAP and a frequent feeling of hunger did not differ between the ^{14}C-UBT (–) and ^{14}C-UBT (+) patients ($p > 0.05$; Table 1).

Table 1: Symptoms of patients at diagnosis with respect to the ^{14}C-urea breath test (UBT)

Gastrointestinal symptoms (n: 537)	Number of patients (%)		
	^{14}C-UBT (–) (301 patients)	^{14}C-UBT (+) (236 patients)	*p*-value
Epigastric pain	236 (78.4)	144 (61)	< 0.0001
Nausea	145 (48.1)	101 (42.8)	N.S.*
Acid regurgitation	79 (26.2)	88 (37.3)	0.006
Epigastric burning	46 (15.2)	46 (19.4)	N.S.
Heartburn	23 (7.6)	39 (16.5)	0.001
Vomiting	43 (14.2)	29 (12.3)	N.S.
Halitosis	41 (13.6)	49 (20.8)	0.03
Early satiety	28 (9.3)	27 (11.4)	N.S.
Recurrent abdominal pain	23 (7.6)	22 (9.3)	N.S.
Feeling of hunger	14 (4.6)	11 (4.7)	N.S.

*N.S. = non-significant.

All ^{14}C-UBT (+) patients (n = 236) were administered an eradication protocol: 156 (66.1%) patients were treated with amoxicillin + clarithromycin + lansoprazole and 80 (33.9%) patients with amoxicillin + metranidazole + lansoprazole. No difference was found in age or gender between treatment protocols at the presentation ($p = 0.34$ and 0.25, respectively).

Regardless of the protocol, 124 of 236 (52.5%) patients were ^{14}C-UBT (–) after the treatment. Treatment success did not differ by age and gender ($p = 0.07$ and 0.5, respectively). Fifty (62.5%) patients treated with the metranidazole protocol had a negative control ^{14}C-UBT after the eradication treatment, compared with 74 (47.4%) patients treated with the clarithromycin protocol ($p = 0.03$).

All gastrointestinal symptoms were compared before and after the eradication treatments, as shown in Table 2. After the eradication treatment, regardless of treatment success, 117 (49.5%) patients were still symptomatic, however, the frequency of total gastrointestinal symptoms were significantly decreased ($p < 0.0001$). The frequency of epigastric pain, epigastric burning, heartburn, acid regurgitation, nausea, vomiting, RAP, early satiety and halitosis were reduced significantly as shown in Table 2.

Table 2: Gastrointestinal symptoms of the ^{14}C-urea breath test (UBT)-positive patients at the presentation and after the eradication treatment independent of the control ^{14}C-UBT results

Gastrointestinal symptoms	Number of patients (%)		
	At presentation	Post-treatment	*p*-value
Total gastrointestinal symptoms	236 (89.1)	117 (49.5)	< 0.0001
Epigastric pain	144 (61)	72 (61.5)	< 0.0001
Nausea	101 (42.8)	42 (35.9)	< 0.0001
Epigastric burning	46 (19.4)	28 (11.8)	< 0.0001
Acid regurgitation	88 (37.3)	38 (32.4)	< 0.0001
Halitosis	49 (20.8)	27 (23)	< 0.0001
Heartburn	39 (16.5)	10 (4.2)	< 0.0001
Vomiting	29 (12.3)	3 (2.5)	< 0.0001
Early satiety	27 (11.4)	13 (11.1)	< 0.0001
Recurrent abdominal pain	22 (9.3)	8 (6.8)	< 0.0001
Feeling of hunger	11 (4.6)	7 (5.9)	N.S.*

*N.S. = non-significant.

After the eradication treatment, the frequency of total gastrointestinal symptoms were decreased significantly in the ^{14}C-UBT (–) patients compared with the ^{14}C-UBT (+) patients ($p < 0.0001$). The frequency of epigastric pain, epigastric burning, heartburn, acid regurgitation, early satiety, halitosis and nausea were significantly reduced in the ^{14}C-UBT (–) patients as shown in Table 3.

Table 3: Gastrointestinal symptoms of patients with respect to control the ^{14}C-urea breath test (UBT) results after the eradication treatment

Gastrointestinal symptoms	Number of patients (%)		
	^{14}C-UBT (+) (n: 112)	^{14}C-UBT (–) (n: 124)	*p*-value
Total gastrointestinal symptoms	78 (85.7)	39 (26.8)	**< 0.0001**
Epigastric pain	48 (52.7)	24 (16.5)	**< 0.0001**
Nausea	30 (33)	12 (8.2)	**0.001**
Epigastric burning	20 (22)	8 (5.5)	**0.003**
Acid regurgitation	25 (27.4)	13 (8.9)	**0.006**
Halitosis	18 (19.7)	9 (7.6)	**0.02**
Heartburn	7 (7.7)	3 (2)	**0.002**
Vomiting	2 (2.1)	1 (0.6)	N.S.*
Early satiety	10 (11)	3 (2)	**0.02**
Recurrent abdominal pain	6 (6.6)	2 (1.3)	N.S.*
Feeling of hunger	4 (4.4)	3 (2)	N.S.*

*N.S. = non-significant.

DISCUSSION

In our study, *H. pylori* infection was found in 43.9% of the children who had gastrointestinal symptoms. After the eradication treatment, the frequency of gastrointestinal symptoms were reduced significantly regardless of the treatment success. Nearly half of the infected children were resistant to the given eradication treatment.

The frequency of gastrointestinal symptoms were significantly reduced with a successful eradication.

Chronic *H. pylori*-associated gastritis is generally asymptomatic, particularly in children (2, 14). Symptomatic diseases associated with the *H. pylori* infection generally arise mainly in adults from long-term infection (14). *H. pylori* infection may cause dyspeptic symptoms through several mechanisms, such as increased gastric acid secretion, persistent and active inflammation of the gastric mucosa, and post-infective motility changes in the gastrointestinal tract, elevated fasting and post-prandial levels of serum gastrin, and decreases in somatostatin secretion (14).

There is conflicting evidence for an association between the gastrointestinal symptoms and *H. pylori* infection in both children and adults (2–11, 15–17). Carvalho *et al* (10) reported no differences among the rates of symptoms between *H. pylori*-infected and non-infected children. Also, Ozen *et al* (18) reported that *H. pylori*-infected children did not complain much more than others of abdominal pain or dyspepsia. Spee *et al* (8) found no evidence of any relationship of RAP, nausea, halitosis, dyspepsia, regurgitation with the *H. pylori* infection in children in a meta-analysis of 38 studies. However, Daugule *et al* (11) reported a higher prevalence of the *H. pylori* infection in children with gastrointestinal symptoms compared with asymptomatic children. In the meta-analysis of Spee *et al* (8), an association between the *H. pylori* infection and both vomiting and upper abdominal pain was found in referred children (but not in children who were seen in primary care). In our study, halitosis, acid regurgitation and heartburn were more prevalent among *H. pylori*-infected patients at the presentation, however, epigastric pain was more prevalent in the ^{14}C-UBT (–) patients. There was no difference in RAP, nausea, vomiting, early satiety or the frequent feeling of hungry prevalence between the ^{14}C-UBT (–) and (+) patients at presentation.

The resolution of dyspeptic symptoms due to a successful *H. pylori* eradication also remains controversial in both children and adults (16, 17). It has been reported that the 'active' component (polymorphonuclear leucocyte infiltration) of gastritis recovers quickly and completely following bacterial eradication, however, lymphocytic infiltrate in the gastric mucosa may persist for several months or even years (19). It has been suggested that these cells can cause alterations in the gastric mucosal function by production of different cytokines. After bacterial eradication, it may take at least 6–12 months for the gastric mucosa to normalize (20). Ashon *et al* (7) reported bacterial eradication had no effect on gastrointestinal symptoms, such as abdominal pain, heartburn and regurgitation, hunger pain, nausea, sensation of fullness, burping or bloating in children. On the other hand, Uc and Chang (9) reported a clear improvement in dyspeptic symptoms after a successful eradication in children. Ozcay *et al* (3) reported that abdominal pain and dyspeptic symptoms were reduced or completely resolved in 75.7% of children after a successful eradication.

A relationship between gastric acid output and improvement of dyspeptic symptoms following *H. pylori* treatment has been reported (17). Also, increased gastric acid secretion associated with the *H. pylori* infection may be suppressed by PPIs, and acid-related dyspeptic symptoms may be relieved in attempts to eliminate *H. pylori* (17).

In our study, the frequency of total gastrointestinal symptoms (except the feeling of frequent hunger) were significantly decreased after the eradication treatment regardless of treatment success. This may be related to the improvement of acid-related dyspeptic symptoms due to PPI treatment. Also, the frequency of total gastrointestinal symptoms were found to be reduced significantly in patients who underwent a successful *H. pylori* eradication. Epigastric pain and burning, nausea, acid regurgitation, halitosis, heartburn and an early feeling of satiety were significantly improved with a successful eradication.

No relationship has been reported previously between the *H. pylori* infection and RAP, and screening for *H. pylori* is not recommended in children with RAP (1, 8). In our study, RAP was not related to the *H. pylori* infection at the presentation, and also after a successful eradication, no significant improvement was seen in RAP. Regardless of treatment success, the frequency of patients with RAP reduced after the eradication treatment, this may be due to use of PPIs or antibiotics.

The relationship between *H. pylori* infection and gastro-oesophageal reflux disease (GERD) remains a matter of controversy. Both aggravation and recovery of oesophagitis after *H. pylori* treatment have been reported in adults (21–24). In children, any association between the *H. pylori* infection and GERD also remains controversial. No association, a positive correlation and protection against GERD have all been reported (22–24). In our study, we found that the frequency of acid regurgitation and heartburn were significantly higher in *H. pylori* (+) patients, and both were reduced after the eradication treatment and also after a successful eradication.

Unfortunately to establish a precise relationship between GERD and *H. pylori* due to these results would not be appropriate, because endoscopic, histopathological and pH monitarization findings were not included to the study.

In previous reports, a possible link between the *H. pylori* infection and halitosis has been postulated. Especially after a successful *H. pylori* eradication, an improvement of halitosis has been reported (6, 25, 26). In our study, halitosis found to be related with the *H. pylori* infection and improved with *H. pylori* eradication. However, defining of halitosis due to patients' complaints, in spite of an objective method as gas chromatography which evaluates volatile sulphur compounds in breath was a limiting factor in our study.

In the developing countries, the prevalence of *H. pylori* infection is still common. In Turkey, the *H. pylori* infection was diagnosed in 50%–56% of 'healthy' children by using the ^{13}C-UBT (18). Also, eradication rates remain low in the developing countries (approximately 50%) (1, 17). Regardless of the treatment protocol, treatment success was 52.5% in our study similar to the previous reports. Eradication rates may differ with the given treatment protocol due to antibiotic resistance. A recent review of primary antimicrobial resistance in *H. pylori* in Turkey demonstrated resistance rates to amoxicillin, clarithromycin and metranidazole of 0.97%, 24.8% and 33.7%, respectively (27). In the previous years, a clarithromycin resistance rate was reported to be 18%–22% in children (3, 28), however, recent studies demonstrated the increased clarithromycin resistance rates (42%–53%) in our country (29, 30). In our study, primary clarithromycin resistance rate was 52.6% similar to the recent reports. The high resistance rates to clarithromycin in our country may be due to the common and uncontrolled use of clarithromycin in children. Primary metranidazole resistance rate of 37.5%, and we found that metranidazole was more effective than clarithromycin in eradication of *H. pylori*.

The study limitations were the following: (a) being a retrospective study; (b) upper gastrointestinal endoscopy, histopathologic examination, *H. pylori* culture were not included in the study; (c) a symptom rating scale to compare the severity of pre- and post-treatment symptoms was not used because of reviewing the records. However, we tried to minimize these limitations as follows: (a) we considered the 'improvement' of any symptom to be complete resolution of the symptom. If the symptom was merely reduced, or reduced immediately after treatment but again relapse, it was not defined as resolution; (b) the symptomatology was reviewed by the same observer.

CONCLUSION

In our study, nearly half of the children with gastrointestinal complaints had the *H. pylori* infection and nearly half of the infected children were resistant to the eradication treatment. Not only a successful eradication but also attempt to eliminate *H. pylori* resulted in a significant reduction of gastrointestinal symptoms.

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