Relationship between Helicobacter pylori Infection and Gastrointestinal Symptoms in Children

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ABSTRACT

Objective: We aimed 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 positivitiy. The frequency of heartburn, acid regurgitation and halitosis ($p = 0.001$, $p = 0.006$, and $p = 0.03$ respectively) were significantly high in ^{14}C-UBT (+) patients, frequency of epigastric pain ($p < 0.0001$) was significantly high in ^{14}C-UBT (-) patients at presentation. ^{14}C-UBT (+) patients were treated with amoxicillin + lansoprazole + clarithromycin (66.1%) / metranidazole (33.9%). After eradication treatment control ^{14}C-UBT were negative in 62.5% of patients treated with the metranidazole, compared with 47.4% of patients treated with the clarithromycin protocol ($p = 0.03$). After eradication treatment, frequency of gastrointestinal symptoms (except 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 ($p = 0.02$), 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, teatment

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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/undeveloped countries. It can persist for a life time, and chronic infection is nearly always accompanied by chronic active gastritis. *H. pylori* infection is usually asymptomatic particularly in children, but may cause serious diseases, such as peptic ulcer disease, non-cardiac gastric adenocarcinomas, and 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 adults. Also the resolution of dyspeptic symptoms after a successful *H. pylori* eradication remains controversial. Also relation of healing of mucosa after 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 primarily admitted or they were 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. Also the records of the ^{14}C-UBT positive patients were reviewed for the given randomised ampirical 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 frequent feeling of hunger were taken into account in the

symptomatology. Localised pain sensation in the epigastric region was considered as epigastric pain. Localised burning sensation in the epigastric region, not radiated up towards the throat was considered as epigastric burning. If the burning sensation was in the chest, radiated up towards to thorat was considered heartburn.

A sudden regurgitation of acid gastric content was considered as acid regurgitation. Inability to finish a normal meal was considered as early satiety (12). Halitosis was defined if patient complaint 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 3 months, at least 3 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 eradication treatment. ^{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: 1) 5-18 years of age, 2) if at least one of the above gastrointestinal symptoms was present for at least 2 months, 3) not treated with antimicrobial drugs or acid-suppressive drugs for at least 1 month prior to the ^{14}C-UBT, 4) naïve for *H. pylori* eradication treatment, 5) if treatment protocol consisted of lansoprazole (1-2 mg/ kg/day, maximum 2x30 mg/day) + amoxicillin (50 mg/kg/day, maximum 2 g/day) + metranidazole (15 mg/kg/day, maximum 1 g/day) or clarithromycin (15-20 mg/kg/day, maximum 1 g/day) for 14 days, twice daily, 6) if symptomatology was noted after treatment, 7) if control ^{14}C-UBT were performed at least 1 months after completing the eradication treatment. Children were excluded from the study if 1) they had a previously known peptic ulcer disease, or no gastrointestinal complaints at presentation, 2) treatment protocol did not include the drugs above 3) eradication treatment was

discontinued or improperly used, 4) after eradication treatment a control ^{14}C-UBT wasn't performed, 5) control ^{14}C-UBT were performed less than 1 month or more than 2 months after completing eradication treatment.

Statistical analyses

Statistical analyses were performed using SPSS software (ver. 17.0). 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 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 presentation ($p > 0.05$). ^{14}C-UBT (+) patients [12 ± 3.3 (range, 5-17.5) years] were older than ^{14}C-UBT (-) patients [11.4 ± 3.4 (range, 5-18) years] at presentation ($p = 0.03$).

In Table 1, the gastrointestinal symptoms of patients are given based on the ^{14}C-UBT results at presentation. Epigastric pain were more frequently observed in ^{14}C-UBT (-) patients as compared with in ^{14}C-UBT (+) patients ($p < 0.0001$). Heartburn, acid regurgitation and halitosis were more frequently observed in ^{14}C-UBT (+) patients as compared with in ^{14}C-UBT (-) patients ($p = 0.001$, $p = 0.006$, $p = 0.03$ respectively). Nausea, vomiting, epigastric burning, early satiety, recurrent abdominal pain (RAP), and a frequent feeling of hunger did not differ between ^{14}C-UBT (-) and ^{14}C-UBT (+) patients ($p > 0.05$; Table 1).

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

Regardless of the protocol, 124 of 236 (52.5%) patients were ^{14}C-UBT (-) after treatment. Treatment success did not differ by age and gender (p = 0.07, 0.5, respectively). Fifty (62.5%) patients treated with the metranidazole protocol had negative control ^{14}C-UBT after 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, but frequency of total gastrointestinal symptoms were significantly decreased (p < 0.0001). Frequency of epigastric pain, epigastric burning, heartburn, acid regurgitation, nausea, vomiting, RAP, early satiety, and halitosis were reduced significantly as shown in Table 2.

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

DISCUSSION

In our study, *H.pylori* infection was found 43.9% of the children who had gastrointestinal symptoms. After eradication treatment, frequency of gastrointestinal symptomps 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 successful eradication.

Chronic *H. pylori*-associated gastritis is generally asymptomatic, particularly in children (2, 14). Symptomatic diseases associated with *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 postprandial levels of serum gastrin, and decreases in somatostatin secretion (14).

There is conflicting evidence for an association between 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 *H. pylori* infection in children in a meta-analysis of 38 studies. However, Daugule et al.(11) reported a higher prevalence of *H. pylori* infection in children with gastrointestinal symptoms compared with asymptomatic children. In the meta-analysis of Spee et al.(8) an association between *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 presentation, but epigastric pain was more prevalent in

^{14}C-UBT (-) patients. There was no difference in RAP, nausea, vomiting, early satiety, or the frequent feeling of hungry prevelance between in ^{14}C-UBT (-) and (+) patients at presentation.

The resolution of dyspeptic symptoms due to successful *H. pylori* eradication also remain 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, but 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 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 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 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 *H. pylori* infection, may be suppressed by proton pump inhibitors (PPIs), and acid-related dyspeptic symptoms may be relieved in attempts to eliminate *H. pylori* (17).

In our study frequency of total gastrointestinal symptoms (except the feeling of frequent hunger) were significantly decreased after 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 successful *H. pylori* eradication. Epigastric pain and

burning, nausea, acid regurgitation, halitosis, heartburn, and an early feeling of satiety were significantly improved with successful eradication.

No relationship has been reported previously between *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 *H. pylori* infection at presentation, and also after a successfull eradication no significant improvement was seen in RAP. Regardless of treatment success, the frequency of patients with RAP reduced after 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 *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 frequency of acid regurgitation and heartburn were significantly higher in H. pylori (+) patients, and both were reduced after eradication treatment and also after a successful eradication. Unfortunately to establish a precise relationship between GERD and *H.pylori* due to these results wouldn't be appropriate, because endoscopic, histopathological and pH monitarisation findings weren't included to the study.

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

In developing countries, prevelance of *H. pylori* infection is still common. In Turkey *H. pylori* infection was diagnosed in 50-56% of 'healthy' children by using the ^{13}C-UBT (18). Also, eradication rates remain low in 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 previous years, clarithromycin resistance rate was reported to be 18 - 22 % in children (3, 28), but recent studies demonstrated an 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 metranidazole was more effective than clarithromycin in eradication of *H. pylori*.

The study limitations were as following; 1) being a retrospective study, 2) upper gastrointestinal endoscopy, histopathologic examination, *H.pylori* culture didn't included to the study, 3) a symptom rating scale to compare the severity of pre- and post-treatment symptoms didn't used because of reviewing the records. But we tried to minimize these limitations as following; 1) 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 relaps, it was not defined as resolution 2) symptomatology was reviewed by the same observer.

CONCLUSION

In our study nearly half of the children with gastrointestinal complaints had *H. pylori* infection and nearly half of the infected children were resistant to 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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Table 1: Symptoms of patients at diagnosis with respect to the ^{14}C-urea breath test (UBT).

	Number of patients (%)		
Gastrointestinal symptoms (n: 537)	**^{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

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

Gastrointestinal symptoms	Number of patients (%)		P value
	At presentation	Post-treatment	
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

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

	Number of patients (%)		
Gastrointestinal symptoms	**^{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