Gastroesophageal reflux disease and Helicobacter Pylori infection in children

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Abstract

Objective. *The main aim of our prospective study was to establish the relationship between Helicobacter pylori (H.pylori) infection and Gastroesophageal reflux disease (GERD) in children population. GERD is a multifactorial disorder characterized by reflux of gastric acid into the esophagus, leading to symptoms, mucosal inflammation and injury. There is a strong and probably causal interrelation between bacterial infection, longstanding GERD/peptic esophagitis and esophageal adenocarcinoma in the future, as a consequence. Given a relatively high prevalence of GERD/peptic esophagitis and bacterial infection in the community and their consequences (peptic esophagitis, Barrett's esophagus and adenocarcinoma), any relationship between these two conditions is likely to be important for all physicians. The relationship between GERD and H.pylori infection is controversial. There are limited published data in children population. The results of previous studies are contradictory and confusions. Adult studies suggested that bacterial infection may protect against GERD by causing atrophic gastritis, which leads to reduced gastric acid secretion. Contrasting views have been reported in small prospective studies on children population.*

Methods. *97 patients with H.pylori infection had esophagogastroduodenoscopy (EGD) with biopsies between 2009 and 2012. Infection with H.pylori was diagnosed by positive culture or from a biopsy sample taken during the endoscopy. Peptic esophagitis was confirmed by endoscopy (macroscopic) as an erosive lesion of the esophageal mucosa (graded by Savary Miller classification). Four weeks after the treatment of bacterial infection (triple therapy), a second EGD with biopsies was performed and the new endoscopic features were noticed.*

Results. *At the first endoscopic examination, esophagitis was presented in 82 of 97 children enrolled in our study. Post treatment, 52 patients with peptic esophagitis had successfully eradicated H.pylori and 12 of those with normal esophagus at the first endoscopy. The eradication rate of H.pylori was higher in patients with normal esophagus (80%) than in those with esophagitis (63%): 12 of 15 versus 52 of 82 ($P < 0.02$). Persistent esophagitis in 24 (29%) children who had esophagitis at the first examination was only related to the initially presence of this condition, before eradication. None one case of peptic esophagitis was recorded after H.pylori eradication in our patients with a normal esophagus at the first endoscopy ($P < 0.01$)*

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and no GERD's complications (esophageal stenosis, Barrett's esophagus or gastric metaplasia) were observed during the study period in the group of patients with peptic esophagitis.

Conclusion. *The findings suggest that treatment of H.pylori infection should be considered in children with concomitant GERD. In light of these results, H.pylori eradication therapy is unlikely to either induce or exacerbate peptic esophagitis.*

Keywords: relationship, H.pylori infection, GERD/peptic esophagitis, eradication, bacterial infection

BACKGROUNDS AND AIMS

GERD is highly prevalent in the pediatric population. In the last years, a potential relationship between *H.pylori* eradication and GERD onset has been claimed. The relationship between GERD and *H.pylori* infection in children remains controversial. There are limited published data in children population. The results of previous studies are contradictory and confusions (1,2,3,4). Adult studies suggested that bacterial infection may protect against GERD by causing atrophic gastritis, which leads to reduced gastric acid secretion. It is well known, in adult population, that gastritis localized in the antrum is associated with hyperacidity, that could be a cause for esophagitis and the gastritis in the corpus, could protect the esophagus from erosions, being associated with hypoacidity. In conclusion, the main mechanism of GERD is the gastric acid hypersecretion, that develops after bacterial cure in adults patients with corpus-predominant gastritis. In addition, esophagitis onset after *H.pylori* eradication in duodenal ulcer or antral gastritis adult patients has been ascribed to a gastric acid hypersecretion, which could develop following body gastritis healing. Contrasting views on this issue have been reported in small prospective studies on children population. Intra-esophageal pH recording studies failed to demonstrated increased acid reflux and peptic esophagitis, following *H.pylori* eradication in children. In contrast, *H.pylori* appeared to be a risk factor for GERD in children. Few studies in children population, have noted positive association between *H.pylori* infection and GERD (5). In only one study, by Rosioru et al. (6), the prevalence of esophagitis was similar in children with GERD either with or without *H.pylori* infection (26% *v* 23%). Few esophageal manometric studies, in adult population, also suggest that bacterial eradication would reduce, rather than favor, acid reflux into the esophagus. Data of clinical studies would suggest that *H.pylori* eradication is not significantly associated with GERD onset and some data suggesting also an advantage in curing the infection when esophagitis is already present in adults (3,4). If eradication of *H.pylori* is indeed associated with an increased incidence of GERD, the increasing use of *H.pylori* eradication could theoretically be responsible for an increased prevalence of GERD's complications like: peptic esophagitis, Barrett's esophagus and esophageal adenocarcinoma in the future, as a consequence. In conclusion, indications for *H.pylori* eradication require clarification in the young (3).

The main aim of our prospective study was to establish the relationship between *H.pylori* infection (as a potential pathogen factor) and GERD in children population. The purpose of this prospective study was to assess the incidence of peptic esophagitis and GERD's complications after eradication of the bacterial infection.

PATIENTS AND METHODS

Patients

All the children and adolescents who were referred for EGD to our clinic during a 4-years period (2009-2012) with typical symptoms of GERD were eligible for this prospective study if they had *H.pylori* infection at endoscopy, received treatment and underwent a second endoscopy to confirm eradication. Frequency Scale for the Symptoms of GERD (FSSG) score, a questionnaire evaluating the symptoms of GERD, was high. Five patients had no post treatment endoscopy. These patients were excluded from this study.

In total, 97 patients 3 to 18 years (mean age, 9.49 years) were included in the study. There were 55 girls and 42 boys. The clinical indications for EGD were as follows: feeding difficulties, vomiting, hematemesis, abdominal pain, increased seizure frequency or weight loss. None one patient at the time of first endoscopy was in treatment for GERD. The patients in

treatment for GERD were not included in our study, as a consequence.

The patients excluded from the study were not different from the studied population with regard to age, gender ratio or presence of symptoms.

Endoscopy

A first EGD was performed in all enrolled children. Reflux esophagitis was confirmed by endoscopy (macroscopic) as an erosive lesion of the esophageal mucosa. Peptic esophagitis was graded by Savary and Miller classification. Esophageal biopsies were not performed. Gastric biopsies (fundus and antrum) were made using a pediatric fibroscop. A second endoscopy was performed 4 weeks after the treatment (antibiotics and antisecretory drugs).

97 children were followed up for a mean of 3.5 months (range, 2-12 months). The study for every patient was terminated when *H.pylori* infection was eradicated. A third endoscopy was performed in those patients with persistent infection 4 weeks after the discontinuation of the second course of treatment (using antibiograms results).

Bacteriologic study

Infection was diagnosed by positive culture or from two gastric biopsies samples taken during the endoscopy one from the fundus and one from the antrum (7) who were immediately placed in saline buffer at 4°C and taken to the laboratory within 1 hour. Bacteriologic study consisted of microscopic examination of biopsies after gram staining, measurement of urease activity (colored reaction in liquid media after 1 hour and after 24 hours of incubation at 37°C) and bacterial culture of mucosal biopsies. Cultures were performed on Colombia agar medium with 10% horse blood, for 3 to 10 days under microaerobic conditions. (3). Children were considered infected when *H.pylori* was present by histologic evaluation or by positive culture from at least one sample. All enrolled patients had *H.pylori* infection. The eradication of infection was defined by negative findings in both bacterial culture and histologic examination. (3).

Treatment

All enrolled patients received 1 to 4 weeks of treatment with two or three drugs according to the current standards or according to observed sensitivity of the strains to antibiotics (amoxicillin, metronidazole or clarithromycin, and antisecretory drugs – proton pump inhibitors like esomeprazole) (8). Children with persistent infection at the second endoscopy underwent a second course of treatment using antibiograms results (3).

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the latest (2008) version of Helsinki Declaration of 1975.

Statistics

Comparisons between esophagitis and *H.pylori* status were made by χ^2 analysis using Fisher exact test. A *P* value of < 0.05 was taken to indicate statistical significance.

RESULTS

By definition, all of the 97 pediatric patients had *H.pylori infection* (positive histologic findings; positive cultures or both). At first endoscopy, 82 of 97 (84%) of the patients had peptic esophagitis (Fig. 1), graded by Savary and Miller classification. At first examination, 66 patients (81.99%) had peptic esophagitis grade I, 11 (14.40%) grade II, 2 (1.66%) grade III and 3 (1.94%) grade IV (Fig. 2). I also mention that all patients had gastritis, but no evidence of ulcers or atrophic gastritis was found by histologic examination.

The mean age of the patients was 9.49 years (range, 3-18 years). There were 55 girls and 42 boys. After the first treatment course, *H.pylori* infection was eradicated in 52 patients with esophagitis. Eradication of *H.pylori* was obtained in 12 of 15 of those with normal macroscopic

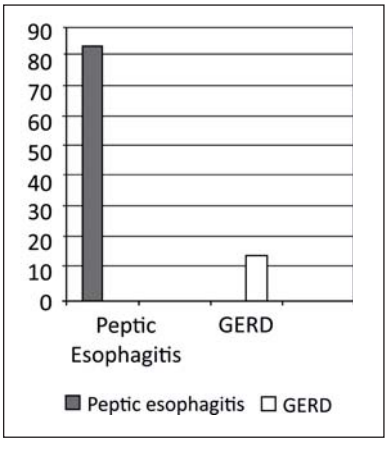

FIGURE 1. *Time of the first endoscopy (Nr.)*

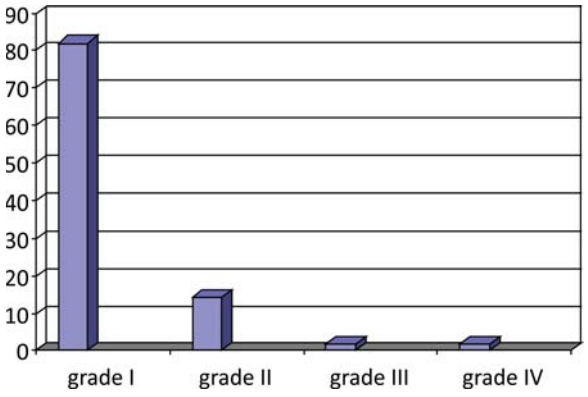

FIGURE 2. *Savary Miller Peptic esophagitis' classification initially (%)*

esophagus. All 15 patients still had a normal esophagus at the post-treatment EGD. The eradication rate of *H.pylori* was higher in patients with normal esophagus (80%) than in those with esophagitis (63%): 12 of 15 versus 52 of 82 (P < 0.02) (Table 1). No GERD's complications (esophageal stenosis, Barrett's esophagus or gastric metaplasia) were observed during the study period. Esophagitis was still present in 24 of 82 (29%) patients who had esophagitis at the first endoscopic examination. Macroscopic healing of esophagitis was defined as complete epithelialization of all esophageal erosive lesions After the first treatment course, persistent esophagitis was noticed in 15 (18.29%) of those with peptic esophagitis grade I, in 4 (4.87%) of those with peptic esophagitis grade II and in all patients with severe esophagitis (grade III and IV) (Fig. 3). At the second endoscopy, the persistence of erosive esophagitis 4 weeks after the completion of treatment was significantly related to the presence of esophagitis before treatment: 24 of 82 versus 0 of 15.

TABLE 1. *After the first treatment course H.pylori eradication*

Total (97)	*H.pylori +*	*H.pylori -*	*Total*
BRGE	3	12	15
Peptic esophagitis	30	52	82

Children with persistent infection at the second endoscopy underwent a second course of treatment. After the second treatment course, *H.pylori* infection was eradicated 3 of 3 of those with normal esophagus and in 30 of 30 with esophagitis. After eradication had been obtained, all 3 patients with GERD still had a normal esophagus at the third EGD. Erosive esophagitis after bacterial eradication was observed at 5 patients at the same severity grade (2 grade III, 3 grade IV). Long-term follow-up data were

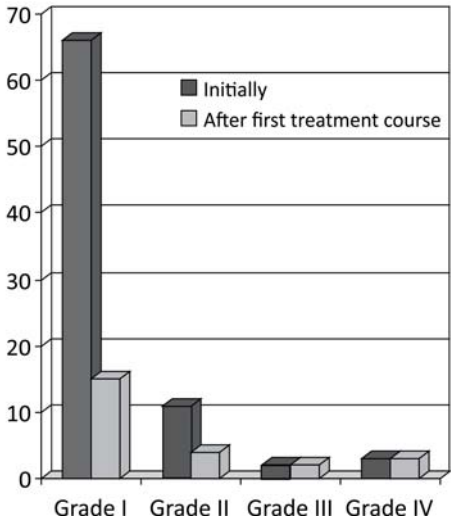

FIGURE 3. *Evolution of peptic esophagitis after first treatment course and Savary Miller classification (Nr.)*

available for these 5 patients with severe esophagitis. Erosive esophagitis after bacterial eradication was observed in 5 of 24 patients with initial esophagitis compared with 0 of 3 in those without esophagitis, after third EGD. No relationship was found between the persistence of esophagitis and eradication of *H.pylori.*

No case of de novo esophagitis was noted in the group of 15 patients with GERD, after *H.pylori* eradication (P<0,01).

DISCUSSION

H.pylori is a clinically important pathogen with a well-known role in the etiology of gastritis or peptic ulcer disease in children and adults.

The presence of *H.pylori* on gastric mucosa is a well-established risk factor for atrophic or metaplastic gastritis, gastric lymphoma or gastric adenocarcinoma (10,11). By contrast, the relation between *H.pylori* infection and GERD's complications: esophagitis, Barrett's esophagus or esophageal adenocarcinoma is still not well understood until now with regards to children population (3,9).

The main aim of this study was to determine whether *H.pylori* eradication induces or worsens GERD in young. No GERD's complications were observed during the study (over a 4 years period).

Adult studies suggested that *H.pylori* infection may protect against GERD by causing atrophic gastritis, which leads to reduced gastric acid secretion (hypochlorhyidria). The rarity of atrophic gastritis in children (no cases were observed in our study) could be an explication (12).

Contrasting views on this issue have been reported in small prospective studies on children population. Few studies in children population, have noted positive association between *H.pylori* infection and GERD. In conclusion, the relationship between these two conditions remains controversial. (13-16)

In one of our study, performed on 361 children with typical symptoms of GERD during a 4 -years period, *H.pylori* infection was found in 97 patients. According to our study we suggest that *H.pylori* infection had a relatively high prevalence and peptic esophagitis is the *most common* type of esophagitis in children (17,18).

Our study clearly shows an absence of association between *H.pylori* eradication and the occurrence of esophagitis. No case of de novo esophagitis was noted in the group of 15 patients with GERD, after *H.pylori* eradication The five cases of persistent esophagitis observed in our study probably can be explained by the tendency for esophagitis to be resistant to treatment. The persistence of esophagitis was significantly related to the presence of erosive esophagitis before treatment, but not to *H.pylori* status.

The last but not the least, several, placebo-controlled, clinical trials have been relatively recently summarized in a meta-analysis including near 4500 patients (19,20).

CONCLUSION

The findings suggest that *H.pylori* infection eradication neither provokes nor worsens peptic esophagitis in children. However, we can not rule out the possibility of late relapse of esophagitis on long term follow-up. In this children population, treating the *H.pylori* infection had no negative consequence in the esophagus. No GERD's complications (esophageal stenosis, Barrett's esophagus or gastric metaplasia) were observed during the study period in the group of patients with peptic esophagitis. Moreover, none one case of de novo esophagitis was noted in the group of 15 patients with GERD. In light of these results, *H.pylori* eradication therapy may be beneficial in children. Treatment of *H.pylori* infection, if indicated, may be given without the fear of aggravating reflux esophagitis In conclusion, indication for *H.pylori* eradication requires clarification in children. Data found that neither reflux symptoms nor erosive esophagitis develop following *H.pylori* eradication. A new meta-analysis could be very important.

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