

Reflux esophagitis and *Helicobacter pylori*: Is there an association in children?

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ABSTRACT

Purpose: The role of *Helicobacter pylori* (*Hp*) in the development of gastroesophageal reflux disease (GERD) remains disputable. This study was planned to determine clinical-epidemic correlations between reflux esophagitis (RE) and *Hp* in older children.

Materials and methods: 308 children with RE and 418 patients with chronic gastritis (CG) without RE between the ages of 12 and 18 were examined. *Hp* was diagnosed by histological (Giemsa and hematoxylin-eosin stain, with evaluation of dissemination grade) and rapid urease test. Subjective symptoms (heartburn, abdominal pain, other

dyspeptic complaints) were analyzed by questionnaire.

Results: *Hp* infection was found in 44.5% of children with RE (no difference in patients without RE), and it does not increase the erosive esophageal defects risk. Clinical symptoms are not connected to this infection in examined patients. The frequency of *Hp* infection decreases with the disease duration increase.

Conclusion: The development of RE is not connected with *Hp*, but the disease course has certain peculiarities in the conditions of *Hp* infection.

Key words: Reflux esophagitis, *Helicobacter pylori* infection, children.

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INTRODUCTION

Over the past decade there has been a significant change in epidemiology of gastrointestinal disorders noted with substantial global increase in gastroesophageal reflux disease (GERD) prevalence [1-4]. Disease often starts in childhood [5-7].

According to the definition established at the Montreal Global Consensus (2005) reflux-esophagitis (RE) is a typical GERD complication [8]. In children frequency of this diagnosis based on endoscopic examination reaches 30% [9].

GERD has a multifactorial genesis, so in the development of this disease many factors play a role (infectious agents, nutrition, physical development, exogenous xenobiotics, stress, physical overexertion, genetic predisposition, and anatomic anomalies) [10]. However, available published results don't allow giving a final assessment to the role of certain etiological agents in the formation and progression of the disease [10-12]. Insufficient data regarding predisposing factors in the pathogenesis of GERD prevents the development of optimal prophylactic measures and treatment of disturbances associated with GERD.

The role of the *Helicobacter pylori* (*Hp*) infection as a possible protective or etiological/triggering factor in GERD pathogenesis is one of the most disputable subjects [13-18]. A significant decrease in the prevalence of *Hp* infection in developed countries, which has negative correlation with GERD incidence, becomes an additional reason for that [4,19]. Republic of Belarus belongs to regions with high *Hp* incidence, but the frequency of typical esophageal complaints increases [20].

However, despite major interest by gastroenterologists and an increasing number of studies there is no unity of opinions about many factors regarding the association of GERD and *Hp*. Additionally, there are only a few pediatric studies investigating this association and those are limited by small sample size.

The objective of this study was to determine the clinical and epidemiological association between RE and *Hp* infection in older children.

MATERIALS AND METHODS

Study group. Children aged between 12 and 18 years, who during esophagogastroduodenoscopy (EGD) revealed inflammatory changes in the mucosa of the esophagus or/and the stomach, were involved in this retrospective case-control study. Indications for EGD were abdominal pain and dyspeptic complaints. All patients were divided in two groups:

308 children with RE (1st group) and 418 patients with microscopically verified CG without RE (2nd group). Children with erosive and non-erosive variants of RE were included in the 1st group. The survey was performed at 3rd and 4th Children's Hospitals in Minsk, Belarus in 2008-2012.

Both groups were evaluated for age and sex (Table 1).

Table 1. Characteristics of the studied groups

Characteristics	Children with reflux-esophagitis (n=308)	Children without reflux-esophagitis (n=418)	P value
Age, years (Median (LQ/UQ): lower quartile/upper quartile)*	16.0 (14.75/17.0)	15.75 (14.5/17.0)	p=0.79
Sex:			
Female	146 (47.4%)	211 (50.5%)	$\chi^2=0.32$ p=0.57
Male	162 (52.6%)	207 (49.5%)	

*- the distribution of the surveyed children by age was not suitable to the normal distribution (according to the W-criterion of the Shapiro-Wilk test, W=0.95 and W=0.93 respectively; p<0.001).

Biopsy specimens were taken from the gastric antrum in all children. The specimens were immediately fixed in 10% buffered formalin solution, embedded in paraffin, cut at 4- to 6- μ m thick, and stained with hematoxylin-eosin (H&A) for histologic evaluation. Diagnosis of CG was made on the basis of a stromal lymphoplasmatic infiltrate of the glandular epithelium. Histological evaluation of gastritis and the *Hp* contamination degree of the gastric mucosa was conducted semiquantitatively in accordance with the Sydney classification of gastritis [20] graded from 0 to 3 (0 grade -the absence of the microorganism, 1 - mild degree, 2 - moderate, and 3 - severe degree of infection). Diagnosis of RE was established in accordance with Los Angeles endoscopic grade system, and in the most of cases confirmed microscopically. The exclusion criteria: treatment with any medications more than seven days over the past 2 months; previous *Hp* eradication; severe neurologic disorders (cerebral palsy, etc.); infections.

Personal data collection for the complaints and anamnesis analysis was carried out by interviewing. As the clinical symptoms associated with RE patients were evaluated for the presence of typical complaints of GERD - heartburn and regurgitation, epigastric abdominal pain and other

dyspeptic complaints (nausea, vomiting, eructation) over six months period. Esophageal symptoms of GERD, as recommended by the Montreal consensus, were considered as positive if the above mentioned complaints were present at least once a week. A similar assessment was used for other symptoms, received by questionnaire. Anamnesis data included disease duration.

HP infection diagnosis

Hp infection was identified based on histology (with Giemsa and H&A stain) and/or rapid urease test (test kit manufactured by UE «SEMPER», Belarus).

Ethical issues

In accordance with Helsinki 2nd Declaration each patient and his parents were informed verbally and in writing about the purpose of study and methods used. All patients and their parents gave the written consent.

Statistical analysis was performed by using the software package Statistica 8.0. Given the abnormal age distribution is presented as median (Me) and lower and upper quartiles (LQ /UQ). To describe the relative frequency of binary features 95% confidence interval (CI) was used. Nonparametric methods of statistical analysis were used: χ^2 test - to evaluate the association between the presence of *Hp* infection and the following features: the frequency of RE, its erosive form, as well as clinical symptoms (heartburn, abdominal pain, dyspeptic complaints); the association of *Hp* infection and duration of illness; Mann-Whitney U-test - to estimate mean age in groups and the relationship of destructive esophageal lesions frequency with the degree of *Hp* infection. All tests were considered as significant at p value <0.05.

RESULTS

According to the results of our study, *Hp* infection was diagnosed in 137 (44.5% (95% CI 38.9-50.2%)) of the patients with RE. *Hp* infection rate in the 2nd group was 179 (42.8% (95% CI 38.1-47.6%)) ($\chi^2=0,20$; $p=0.66$) (Figure1).

Further analysis showed that male patients with RE had *Hp* infection more often than females, but difference was no statistically significant (Table 2).

Erosive lesions of the esophagus (A-D grade esophagitis) were detected in 50.5% (95% CI 44.9-56.1%) of surveyed children. Among *Hp*-positive children with RE frequency of destructive esophageal

lesions was slightly higher compared to the *Hp*-negative patients (51.8% and 50.9% respectively, $p=0.89$). Furthermore, it does not depend on the extent of bacterial infection ($p=0.81$).

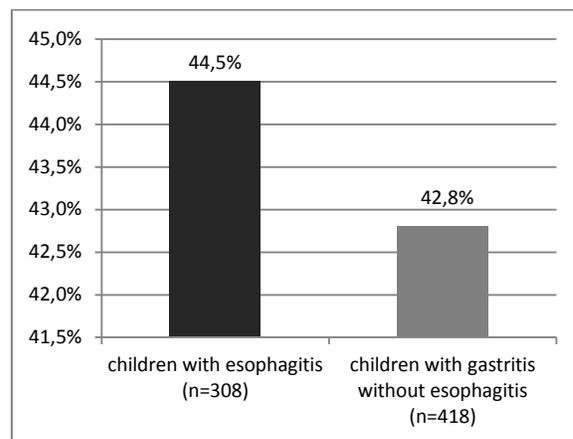


Figure 1. *Hp*-infection incidence rate in comparing groups.

Table 2. Comparison of *Hp*-positive vs *Hp*-negative patients with RE.

Characteristics	<i>Hp</i> -positive (n=137) No. / % (95% CI)	<i>Hp</i> -negative (n=171) No. / % (95% CI)	P value (χ^2)
Sex			
Male	79 / 57.7% (48.9-66.1%)	83 / 48.5% (40.8-56.3%)	$\chi^2=2.54$; P=0.11
Female	58 / 42.3% (34.0-51.1%)	88 / 51.5% (43.7-59.2%)	
RE form			
Erosive	71 / 51.8% (43.1-60.4%)	84 / 50.9% (43.7-58.6%)	$\chi^2=0.03$; P=0.89
Non-erosive	66 / 48.2% (39.6-56.9%)	81 / 49.1% (41.2-57.0%)	
Symptoms			
Heartburn (regurgitation)	93 / 67.9% (59.4-75.6%)	109 / 63.7% (56.1-70.9%)	$\chi^2=0.58$; P=0.45
Epigastric pain	109 / 79.6% (71.8-86.0%)	131 / 76.6% (69.5-82.7%)	
Other dyspeptic complaints	84 / 61.3% (52.6-69.5%)	95 / 55.6% (47.8-63.1%)	$\chi^2=0.39$; P=0.53 $\chi^2=1.04$; p=0.31
Duration of illness			
< one year	30 / 57.7% (43.2-71.3%)	22 / 42.3% (28.7-56.8%)	$\chi^2=4.42$; p=0.04
> one year	107 / 41.8% (35.7-48.1%)	149 / 58.2% (51.9-64.3%)	

The results of main symptoms comparison in *Hp*-positive and *Hp*-negative patients with RE demonstrated a slight increase in the frequency of heartburn and epigastric pain in the *Hp*-positive

children, but the differences in the frequency of various clinical symptoms were not significant.

Further analysis showed that the incidence of *Hp* infection decreased with increasing of disease duration, the difference was statistically significant ($p=0.04$).

DISCUSSION

There have been theoretical attempts to establish *Hp* infection involvement in the pathophysiology of GERD [3, 10].

As evidence of the protective role of *Hp* in GERD, the following arguments are described: the development of *Hp*-associated gastritis in the fundus is accompanied by a decrease in the hydrochloric acid secretion (by inhibiting the production of histamine along with increased synthesis of interleukin (IL) - 1β and tumor necrotizing factor (TNF- α)); proximal gastritis improves the gastroesophageal junction barrier function; hypergastrinemia associated with *Hp* infection leads to increased pressure of the lower esophageal sphincter (LES), high urease activity of *Hp* partially neutralizes the aggressive action of hydrochloric acid; *Hp* can increase antisecretory effect of main antisecretory drugs - proton pump inhibitors [14, 15, 18].

On the other hand, there are explanations of *Hp* infection as a factor contributing to the activation of pathophysiological mechanisms of GERD: inflammation, extending to the stomach cardia, leading to decreased LES pressure; antrum predominant *Hp* gastritis increases gastric secretion, and also delayed gastric emptying; *Hp* cytotoxins cause damage to the esophageal epithelium, activation of apoptosis and increase the risk of carcinogenesis [3, 10, 17, 18].

As follows from our results, the development of esophagitis was not accompanied by changes in the frequency of *Hp* infection compared with patients without RE.

Published data presented from previous studies conducted in children and adults is controversial. Thus, the few studies in pediatric patients with RE showed that *Hp* infection was more common [21, 22] or its frequency did not differ from children without RE [23]. For example, Moon et al. [22] reported a high (81.3%) risk of RE development among the *Hp*-positive children compared with 38.1% in the *Hp*-negative patients. Data published about adults is ambiguous and indicates a lack of association with RE and *Hp* infection [24, 25], reflect reverse [26, 27] or direct [28] relationship between the infection frequency and the esophageal inflammation development.

The results of our study do not support the participation of *Hp* infection in the pathogenesis of more severe esophageal damage. The published research data does not provide an unambiguous assessment of this relationship [9, 23-28].

High frequency of epigastric pain in patients with RE may reflect that they have a combined pathology of the esophagus and stomach, which is typical [9].

Other researchers also found no differences in clinical presentation, depending on the availability of *Hp* infection, but such an assessment was carried out mainly after *Hp* eradication [29-31].

It can be assumed that the reduction of *Hp* infection with increasing disease duration in patients with RE is associated with the active treatment of *Hp* in connection to concomitant gastroduodenal pathology. However, the available data on the increased risk of RE after the elimination of *Hp* infection is controversial, which indicates the need for further study of this relationship in pediatrics [29-31].

CONCLUSIONS

Thus, there was no clear association between reflux esophagitis and *H. pylori* infection. Moreover, the severity of inflammation and the clinical symptoms frequency were also not associated with *Hp* infection incidence rate. Meanwhile, in patients with a long medical history *Hp* infection is rare. Further research is required to establish the role of *Hp* in the occurrence and progression of GERD, the debut of which often falls on the pediatric population.

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