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THE INFLUENCE OF *HELICOBACTER PYLORI* ERADICATION THERAPY ON THE COURSE OF GASTROESOPHAGEAL REFLUX DISEASE IN SCHOOL-AGE CHILDREN

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Abstract. Introduction. Data on the role of *Helicobacter pylori* (Hp) in the development of gastroesophageal reflux disease (GERD) are contradictory; most researchers believe that Hp infection has a protective effect on the incidence of GERD. Ambiguous results have also been obtained regarding the effect of *H. pylori* eradication on the development of GERD, reflux esophagitis and symptoms associated with reflux. Most meta-analyses have found no significant differences in the development of GERD after *H. pylori* eradication between patients with eradication and patients with persistent infection. But a number of studies have reported a significant increase in the risk of GERD after successful eradication therapy. Most studies were conducted on a cohort of adult patients; data on the effect of *H. pylori* on the course of GERD in children are fragmentary. **Objective.** To evaluate the effect of eradication therapy on the course of gastroesophageal reflux disease in school-age children. **Materials and methods.** The study included 55 children from 7 to 17 years 11 months (11.4 ± 2.1 years) with an erosive form of gastroesophageal reflux disease. Three observation groups were formed: first — *H. pylori*-positive patients with eradication therapy; second — *H. pylori*-positive patients without eradication therapy; third — *H. pylori*-negative patients. The dynamics of clinical symptoms and erosive changes in the esophagus were assessed. **Results.** When comparatively assessing the clinical course of GERD in the groups of *H. pylori*-infected and *H. pylori*-negative patients, no significant differences were identified. Heartburn and epigastric pain were noted with equal frequency in both groups, belching was significantly more often observed in the group of *H. pylori*-negative patients, and vomiting, on the contrary, was slightly more common in the group of *H. pylori*-positive patients. The frequency of endoscopic signs of relapse of erosive esophagitis after 12–24 months was also comparable in the compared groups: 7/20 (35.0%) in the group with eradication therapy and 8/20 (40.0%) without eradication therapy. At the same time, the lowest relapse rate of 4/14 (26.8%) was noted in the group of *H. pylori*-negative patients. **Conclusions.** *Helicobacter pylori* does not have a significant protective or negative effect on the course of the erosive form of gastroesophageal reflux disease in school-age children.

Keywords: gastroesophageal reflux disease, children, *H. pylori*

ВЛИЯНИЕ ЭРАДИКАЦИОННОЙ ТЕРАПИИ *HELICOBACTER PYLORI* НА ТЕЧЕНИЕ ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНИ У ДЕТЕЙ ШКОЛЬНОГО ВОЗРАСТА

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Резюме. *Введение.* Данные о роли *Helicobacter pylori* (Hp) в развитии гастроэзофагеальной рефлюксной болезни противоречивы. Большинство исследователей считают, что инфекция *H. pylori* оказывает защитный эффект на заболеваемость гастроэзофагеальной рефлюксной болезнью (ГЭРБ). Неоднозначные результаты получены и в отношении влияния эрадикации *H. pylori* на развитие ГЭРБ, рефлюкс-эзофагита и симптомов, связанных с рефлюксом. В большинстве метаанализов не выявлено существенных различий в развитии ГЭРБ после эрадикации *H. pylori* между пациентами с эрадикацией и пациентами с персистирующей инфекцией. Но в ряде работ сообщено о значительном повышении риска ГЭРБ после успешной эрадикационной терапии. Большинство исследований проведено на когорте взрослых пациентов. Данные о влиянии *H. pylori* на течение ГЭРБ у детей фрагментарные. **Цель** — оценить влияние эрадикационной терапии на течение гастроэзофагеальной рефлюксной болезни у детей школьного возраста. **Материалы и методы.** В исследование включено 55 детей от 7 до 17 лет 11 месяцев (средний возраст 11,4±2,1 года) с эрозивной формой гастроэзофагеальной рефлюксной болезни. Сформировано три группы наблюдения: первая — *H. pylori*-позитивные пациенты с проведенной эрадикационной терапией, вторая — *H. pylori*-позитивные пациенты без эрадикационной терапии, третья — *H. pylori*-негативные пациенты. Оценивалась динамика клинических симптомов и эрозивных изменений в пищеводе. **Результаты.** При сравнительной оценке клинического течения ГЭРБ в группах *H. pylori*-инфицированных и *H. pylori*-негативных пациентов значительных отличий не выявлено. Изжога и эпигастральная боль отмечались с равной частотой в обеих группах. Отрыжка достоверно чаще отмечалась в группе *H. pylori*-негативных пациентов, а рвота, наоборот, несколько чаще в группе *H. pylori*-позитивных пациентов. Частота эндоскопических признаков обострения эрозивного эзофагита через 12–24 месяца была также сопоставима в сравниваемых группах: 7/20 (35,0%) в группе с проведенной эрадикационной терапией и 8/20 (40,0%) без эрадикационной терапии. При этом наименьшая частота рецидивов 4/15 (26,8%) отмечена в группе *H. pylori*-негативных пациентов. **Выводы.** Эрадикация *H. pylori* не оказывает значимого протективного или негативного эффекта на течение эрозивной формы гастроэзофагеальной рефлюксной болезни у детей школьного возраста.

Ключевые слова: гастроэзофагеальная рефлюксная болезнь, дети, *H. pylori*

INTRODUCTION

There are conflicting data on the role of *H. pylori* in the development of gastroesophageal reflux disease (GERD). In 1997, J. Labenz et al. first suggested the hypothesis that eradication of *H. pylori* could lead to the development of reflux disease. And over the last 30 years, many studies have shown that *H. pylori* infection is negatively correlated with GERD. Moreover, most researchers believe that *H. pylori* infection has a protective effect on the incidence of GERD in general [1–3].

Conflicting results have also been obtained regarding the impact of *H. pylori* eradication in relation to the development of GERD, reflux esophagitis and reflux-related symptoms [4–6]. Xie et al. performed a meta-analysis of cohort studies and reported a significantly increased risk of GERD in patients with successful eradication compared to those with failed eradication (relative risk (RR) 1.70, 95% confidence interval (CI) 1.30–2.23), and a significantly increased risk in patients receiving eradication therapy compared to those receiving placebo (RR 1.99, 95% CI 1.23–3.22) [7]. One recent meta-analysis from 2020 also showed that *H. pylori* eradication therapy increased the risk of reflux esophagitis whether there were previous

cases of esophagitis (OR 1.46, 95% CI 1.16–1.84, $p=0.01$) or *de novo* reflux esophagitis (OR 1.42, 95% CI 1.01–2.00, $p=0.03$). This fact was specific for all studies, especially in Western populations [8]. However, most meta-analyses have not found significant differences in the development of GERD after *H. pylori* eradication between patients with eradication and patients with persistent infection [9–11]. Nevertheless, Maastricht VI, recommends eradication therapy for patients with GERD, taking into account that *H. pylori* is a first class carcinogen [12]. As for children, the relationship between *H. pylori* and diseases of the upper digestive tract is probably even more complex. Thus, in contrast to adults, there is no association between *H. pylori* and functional dyspepsia [13]. Most of the works devoted to the relationship between GERD and *H. pylori* in children were performed in 2000–2010. A. Moon et al. (2009), in contrast to adults, showed a negative effect of *H. pylori* on the formation of reflux esophagitis in paediatric patients (mean age 8.2 years), the odds ratio was 5.79 compared to *H. pylori*-negative patients [14]. J. Brazowski et al. showed that *Helicobacter pylori* infection among children with acid gastroesophageal reflux does not affect the

prevalence of esophagitis. Thus, 13.8% of children in the group with *H. pylori* infection and 18.3% in the group without infection had esophagitis [15]. S.E. Zagorsky et al. also did not find any correlation between clinical symptoms of GERD, *H. pylori* and increased risk of erosive-ulcerative lesions of the oesophagus in children and adolescents. The authors based their study on medical check-ups of 300 patients and *H. pylori* [16]. Paediatric clinical guidelines for patients do not include recommendations for eradication therapy in children with GERD, resulting in the necessity to make an independent decision on eradication therapy in this group of patients [17]. Thus, studies on the relationship between GERD and *H. pylori* infection remain relevant.

AIM

To evaluate the effect of eradication therapy on the course of gastroesophageal reflux disease in school children.

MATERIALS AND METHODS

The study included 55 children from 7 to 17 years 11 months (11.4 ± 2.1 years) with erosive form of gastroesophageal reflux disease. The main inclusion criteria: newly diagnosed symptoms of dyspepsia, erosive changes in the oesophagus according to fibrogastroduodenoscopy in children. Helicobacteriosis was diagnosed on the basis of a positive result of histological and/or rapid urease test ("Helicobacter-test" of the Research Institute of ECF, St. Petersburg). Initially all patients were divided into two groups: the first — *H. pylori*-positive (40 children), the second — *H. pylori*-negative

(15 children). Further, patients were divided into two more groups (20 patients in each), depending on the treatment tactics. Additional inclusion criteria for the first group: eradication therapy, control endoscopic examination in 12–24 months, absence of *H. pylori* according to histological or rapid urease test. Additional inclusion criteria in the second group: absence of eradication therapy, control endoscopic examination in 12–24 months. The final comparison was carried out among three groups of patients: the first — *H. pylori*-positive with eradication therapy (*H. pylori*+, eradication therapy+), the second — *H. pylori*-positive without eradication therapy (*Hp*+, eradication therapy-), the third — *H. pylori*-negative patients (*Hp*-). The dynamics of clinical symptoms and erosive changes in the oesophagus were evaluated. All obtained data were statistically processed by means of STATISTICA v.6.1 (StatSoft Inc.) application software package. Significance analysis of differences in qualitative features was performed using the χ^2 criterion. Differences at $p < 0.05$ were considered as significant.

RESULTS

No significant differences were found between clinical features of GERD in *Hp*-infected and *Hp*-negative patients. Heartburn and epigastric pain were noted with equal frequency in both groups. Belching was significantly more frequent in the group of *Hp*-negative patients, and vomiting, on the contrary, was slightly more frequent in the group of *Hp*-positive patients. In addition, stool disorders in the form of constipation, diarrhoea and their combination were significantly

Table 1. Comparative characteristics of symptoms in the groups of *Hp*-positive and *Hp*-negative patients with the erosive form of gastroesophageal reflux disease

Таблица 1. Сравнительная характеристика симптомов в группах *Hp*-положительных и *Hp*-отрицательных пациентов с эрозивной формой гастроэзофагеальной рефлюксной болезни

Симптом / Symptom	<i>Hp</i> -положительные / <i>Hp</i> -positive (n=40)	<i>Hp</i> -отрицательные / <i>Hp</i> -negative (n=15)	p
Эпигастральная боль / Epigastric pain	36 (90,0%)	14 (93,3%)	0,702
Изжога / Heartburn	15 (37,5%)	7 (46,6%)	0,537
Тошнота / Nausea	18 (45,0%)	3 (20,0%)	0,090
Отрыжка / Burping	12 (30,0%)	9 (60,0%)	0,042
Рвота / Vomiting	7 (17,5%)	0 (0,0%)	0,083
Раннее насыщение / Early satiation	2 (5,0%)	1 (6,6%)	0,809
Нарушения стула (запоры/диарея) / Of stool disorders (constipation/diarrhea)	7 (17,5%)	8 (53,3%)	0,008

Table 2. Dynamics of the main symptoms before and after treatment in the compared groups

Таблица 2. Динамика основных симптомов до и после лечения в сравниваемых группах

Группы наблюдения / Monitoring groups	Симптом / Symptom	До лечения / Before treatment	После лечения / After treatment	p
Нр+ эрадикационная терапия + / Нр+ eradication therapy +	Боли / Pain	19 (95,0%)	20 (100,0%)	0,312
	Изжога / Heartburn	6 (30,0%)	3 (15,0%)	0,256
	Отрыжка / Belching	6 (30,0%)	6 (30,0%)	1,000
	Тошнота / Nausea	10 (50,0%)	6 (30,0%)	0,197
	Рвота / Vomit	3 (15,0%)	0 (0,0%)	0,072
	Чувство раннего насыщения / Feel- ing of early satiety	0 (0,0%)	0 (0,0%)	–
	Нарушения стула* / Stool disorders*	3 (15,0%)	1 (5,0%)	0,292
Нр+ эрадикационная терапия– / Нр+ eradication therapy–	Боли / Pain	17 (85,0%)	16 (80,0%)	0,678
	Изжога / Heartburn	9 (45,0%)	8 (40,0%)	0,750
	Отрыжка / Belching	6 (30,0%)	6 (30,0%)	1,000
	Тошнота / Nausea	8 (40,0%)	5 (25,0%)	0,312
	Рвота / Vomit	4 (20,0%)	0 (0,0%)	0,036
	Чувство раннего насыщения / Feel- ing of early satiety	2 (10,0%)	2 (10,0%)	1,000
	Нарушения стула* / Stool disorders*	4 (20,0%)	4 (20,0%)	1,000
Нр–	Боли / Pain	14 (93,3%)	13 (86,6%)	0,736
	Изжога / Heartburn	7 (46,6%)	8 (53,3%)	0,744
	Отрыжка / Belching	9 (60,0%)	4 (26,6%)	0,092
	Тошнота / Nausea	3 (20,0%)	2 (13,3%)	0,633
	Рвота / Vomit	0	1 (6,7%)	0,312
	Чувство раннего насыщения / Feel- ing of early satiety	1 (6,7%)	0 (0,0%)	0,312
	Нарушения стула* / Stool disorders	8 (53,3%)	2 (13,3%)	0,029

* Запор и/или диарея.

* Of stool disorders (constipation/diarrhea).

Table 3. Frequency of exacerbations according to fibrogastroduodenoscopy in the compared groups after 12–24 months

Таблица 3. Частота обострений по данным фиброгастродуоденоскопии в сравниваемых группах через 12–24 месяца

Стадия заболевания / Stage of the disease	Группа 1 (Нр+, эрадикационная терапия+) / Group 1 Нр+ eradication therapy + (n=20)	Группа 2 (Нр+, эрадикационная терапия–) / Group 2 Нр+ eradication therapy– (n=20)	Группа 3 / Group 3 (Нр–) (n=15)
Обострение / Aggravation	7 (35,0%)	8 (40,0%)	4 (26,8%)
Ремиссия / Remission	13 (65,0%)	12 (60,0%)	11 (73,2%)
p	p ₁₋₂ =0,744		p ₁₋₃ 0,600 p ₂₋₃ =0,051

more frequent in the group of *Hp*-negative patients. The results are presented in Table 1.

Subsequently, there was evaluated the dynamics of the main clinical symptoms in 12–24 months. The proportion of patients with complaints of heartburn, nausea, vomiting and stool disorders slightly decreased in the group of *Hp*-positive patients with the course of eradication therapy after the control period. However, the differences were statistically unreliable. The dynamics of symptoms in two other groups (*Hp*-negative patients and *Hp*-positive patients without eradication therapy) was also insignificant. Significant differences concerned individual symptoms only. The results are presented in Table 2.

The assessment of control endoscopic examination showed that the frequency of recurrence of erosive esophagitis in the group of *Hp*-negative patients without eradication therapy was 8/20 (40,0%), which corresponded to the frequency of recurrence in the group of *Hp*-positive patients with eradication therapy — 7/20 (35,0%) ($p=0,744$). At the same time, the frequency of exacerbations was slightly lower in the group of *Hp*-negative patients — 4/15 (26.8%). The results are presented in Table 3.

DISCUSSION

No significant differences were found between *Hp*-positive and *Hp*-negative patients when assessing the severity of clinical symptoms of GERD. Epigastric pain and heartburn were noted with equal frequency in the groups of *Hp*-positive and *Hp*-negative patients. Belching was more frequent among GERD symptoms in *Hp*-negative patients. Associated stool disorders in the form of constipation, diarrhoea and their combination were also more characteristic for *Hp*-negative patients. Significant differences in the dynamics of symptoms in 12–24 months in the groups of *Hp*-positive patients after eradication therapy and without it were not observed.

The frequency of endoscopic signs of recurrence of erosive esophagitis after 12–24 months was also similar in the compared groups: 7/20 (35,0%) in the group with eradication therapy and 8/20 (40,0%) without eradication therapy. The lowest recurrence rate of 4/15 (26.8%) was observed in the group of *Hp*-negative patients. Thus, eradication therapy had no significant positive or negative effect on the recurrence rate in children with erosive GERD.

CONCLUSION

H. pylori eradication has no significant protective or negative effect on the course of erosive gastroesophageal reflux disease in school children.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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