

RESEARCH ARTICLE

Risk of Gastric Cancer in Children with *Helicobacter pylori* Infection

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) is the most common chronic infectious agent in the stomach. Most importantly, it may lead to atrophy, metaplasia and cancer. The aim of this study was to investigate the incidence of *H. pylori* infection and to detect early mucosal changes that may lead to malignant degeneration in children. **Materials and Methods:** Children who underwent upper gastrointestinal endoscopy were included. Familial history of gastric cancer was noted. Endoscopic examinations were performed by a single pediatric gastroenterologist. A minimum of three biopsy samples were collected during endoscopy. The patients were accepted as *H. pylori* infected if results of biopsies and rapid urease test were both positive. Biopsies were evaluated for the presence and degree of chronic inflammation, the activity and severity of gastritis, glandular atrophy and intestinal metaplasia. **Results:** A total of 750 children (388 boys, 362 girls) were evaluated in our study, with a mean age of 10.1 years. A total of 390 patients (52%) were found to be infected with *H. pylori*. Among the *H. pylori* infected patients, 289 (74%) were diagnosed to have chronic superficial gastritis, 24 (6.2%) had gastric atrophy. Most strikingly, intestinal metaplasia was observed in 11 children, all were in the *H. pylori* positive group. There was no difference in the mean of age, gender and socioeconomic class between *H. pylori* infected and non-infected groups. The frequency of gastric cancer in family members (4 in number) was higher in patients with *H. pylori* infection. No gastric cancer case was reported from the parents of non-infected children. The worst biopsy parameters (atrophy and metaplasia) were improved after *H. pylori* eradication on control endoscopy. **Conclusions:** The current study shows a higher prevalence of familial history of gastric cancer in *H. pylori* infected children. Intestinal metaplasia was also higher in the infected children. Eradication of *H. pylori* infection for this risk group may prevent subsequent development of gastric cancer.

Keywords: Children - endoscopy - gastric cancer - *H. pylori* - metaplasia - prevention

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Introduction

Helicobacter pylori (*H. pylori*) is the most common chronic infectious agent worldwide both in adults and children. It is usually acquired during early years of childhood (Vandenplas, 2001). Although the prevalence of *H. pylori* infection is decreasing in northern and western European countries, the infection is still common in southern and eastern parts of Europe and Asia. Developing countries have *H. pylori* prevalence rate of 80% as compared to developed countries (20-50%) (Everhart, 2000). Prevalence among 3-12 years old children is between 18.2%-63% (Ertem et al., 2003). Nonspecific symptoms may be present in *H. pylori* infected children such as epigastric pain, nausea, anorexia, iron deficiency anemia and hematemesis. Most of the infected children may be asymptomatic or degree of symptoms may be unrelated to underlying peptic disease (Iwańczak et al., 2014). *H. pylori* is the causative agent of gastritis, peptic ulcer disease, and also infected gastric mucosa undergoes changes that may lead to atrophy, metaplasia and cancer at

an older age. Hence it was classified as class I carcinogen by the World Health Organization in 1994 (IARC working group, 1994).

Our aim was to investigate the incidence of *H. pylori* infection in pediatric patients having diagnostic upper gastrointestinal endoscopy and to detect early mucosal changes that may lead to malignant degeneration in the future. We also tried to identify gastric cancer history in family members of *H. pylori* infected children in order to follow up those children closely.

Materials and Methods

From March 2011 to March 2014, subsequent children aged between 1 to 18 years who underwent upper gastrointestinal endoscopy at our department were included in the study. Indications for endoscopy were upper gastrointestinal symptoms such as recurrent abdominal pain, retrosternal pain, abdominal distension, nausea, vomiting, belching, regurgitation and also the presence of anemia and growth retardation. Children with

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known chronic gastrointestinal diseases and the ones who used acid suppressing agents, antibiotics, nonsteroidal anti-inflammatory drugs, immuno-suppressive drugs or steroids within the previous month were excluded. Parents were asked for the presence of physician diagnosed gastric cancer history in themselves or their primary relatives. Socioeconomic and environmental factors of the families and growth parameters of the children were also noted.

The endoscopic examinations were performed by a single pediatric gastroenterologist who was experienced in pediatric gastrointestinal endoscopy. Minimum three biopsy samples were collected during endoscopy from the corpus and the antrum. One sample from the antrum was used for an immediate rapid urease test. Biopsies were stained with hematoxylin/eosin and modified Giemsa, and studied by light microscopy. The patients were accepted as *H. pylori* infected if results of biopsies and rapid urease test were both positive and noninfected if both results were negative. The ones who had only one positive test result were excluded.

Biopsies were evaluated for the presence and degree of chronic inflammation, the activity and severity of gastritis, glandular atrophy and intestinal metaplasia according to updated Sydney system (0=absent, 1=mild, 2=moderate and 3=marked). Loss of the glandular tissue was noted as glandular atrophy. Formation of intestinalized glands only in the foveolar region of the gastric glands (incomplete intestinal metaplasia) or involving the entire glands (complete intestinal metaplasia) was also reported.

All of *H. pylori* infected cases were treated with standard treatment protocol (double antibiotic therapy, Amoxicillin and Clarithromycin for two weeks, associated with proton pump inhibitors (PPI) for four weeks. Our aim was to eradicate *H. pylori* infection and to follow up the treated children afterwards.

Mean, standard deviation, proportion and frequency were used in descriptive statistics. Independent sample T-Test was used in the analysis of quantitative data. Chi-square test was used to analyse qualitative data and Fischer's exact test was used where the conditions for using Chi-square test were not met. *p* values <0.05 were considered statistically significant

Results

A total of 750 children (388 boys, 362 girls) constituted the study, with a mean age of 10.1 years. A total of 390 patients (52%) were found to be infected with *H. pylori*. The prevalence of *H. pylori* infection increased with age from 21.3 % under 3 years of age to 72% after age 15 years.

Among the *H. pylori* infected patients, 289 (74%) were diagnosed to have chronic superficial gastritis. Chronic atrophic gastritis was rare, only 24 (6.2%) of the *H. pylori* infected patients had gastric atrophy. Intestinal metaplasia was also rare, observed in 2.8% of *H. pylori* positive cases (Table 1).

Associations of *H. pylori* positivity with age, gender, socioeconomic status and history of gastric cancer in first-degree family members were evaluated. There was no difference in the mean of age, gender and socioeconomic

Table 1. The Pathological Classification of *Helicobacter pylori* Positive Children (n=390)

	Absent -n (%)	Mild -n (%)	Moderate -n (%)	Marked -n (%)
Inflammation	101 (25.9%)	195 (50%)	94 (24.1%)	0
Activity	77 (19.8%)	199 (51%)	110 (28.2%)	4 (1%)
Atrophy	366 (93.8%)	16 (4.1%)	8 (2.1%)	0
Metaplasia	379 (97.2)	9 (2.3%)	2 (0.5%)	0

class between *H. pylori* infected and noninfected groups ($p>0.05$). The frequency of gastric cancer in family members was higher in patients with *H. pylori* infection, compared to noninfected patients although the number was low. A total of four cases of gastric cancer was detected from family evaluation. All of the cases were from the *H. pylori* infected patients' families (one father, one mother, two grandparents that lived in the same household). No gastric cancer case was reported from the parents of noninfected children.

The prevalence of mucosal inflammation was higher in *H. pylori*-infected patients as expected (74% vs 5.2%). Activity and severity of gastritis was also higher in the *H. pylori*-infected group (79% vs 6.9%). Gastric atrophy and metaplasia was rare in both groups although more cases were identified in *H. pylori* positive group. Twenty-four patients found to have focal glandular atrophy among infected children (6.2%) only one case was noted to have mild partial atrophy in uninfected group. Intestinal metaplasia was observed in 11 children, all were in the *H. pylori* positive group ($p<0.05$). No case of gastric cancer was detected in the study group.

When we looked at the four children with family history of gastric cancer, one case was found to have mild focal glandular atrophy and mild intestinal metaplasia. There was no more specific pathologic finding in the biopsies of other children with family history of gastric cancer when compared with the rest of the *H. pylori* infected cases.

All of the children with *H. pylori* gastritis had eradication therapy. Cases with gastric atrophy and glandular metaplasia had endoscopic evaluation one year later. All of the findings were found to be regressed, no gastric atrophy and/or metaplasia was present and only one *H. pylori* infection was detected in control endoscopy.

Discussion

H. pylori is still the most common chronic infectious agent all over the world. It infects adults as well as the children (Axon, 2014). Moreover the infection is mostly acquired during childhood and persists lifelong. High risk of intrafamilial infection was shown in previous studies (Mourad-Baars et al., 2010; McMillan et al., 2011). It causes gastritis, peptic ulcer disease and may lead to chronic pathological changes in gastric mucosa that may predispose to development of gastric cancer in time (Piazuelo et al., 2013).

The proportion of infected children increases with age. Vanderpas et al. (2014) found that the prevalence of *H. pylori* was 18.2% in children aged <6 years and 49.3% in adolescents aged 12-17 years. Ertem et al. (2013) found

that the prevalence was 18.2% under 4 years, 41% at 4-6 years, 48.6% at 6-8 years, 50% at 8-10 years, and 63% at 11-12 years of age. In our study group (children with upper gastrointestinal complaints) biopsy proven *H. pylori* incidence was 52%.

The pathological changes caused by *H. pylori* infection in the gastric mucosa of the children are bacterial colonisation, progressive inflammation, glandular atrophy and intestinal metaplasia. Atrophy and intestinal metaplasia can be regarded as precancerous lesion for gastric cancer (Correa, 1983). In a study from China prevalence of active inflammation was found 26.9%, chronic superficial gastritis was 41.9%, atrophic gastritis was 21.7% in *H. pylori* infected children (Yu et al., 2014). In our study inflammation was detected in 74.1%. Although in some studies gastric atrophy was reported up to 72% in *H. pylori* positive children, from many countries atrophy was shown in limited cases varying from 0 to 4% (Campbell et al., 2001; Ozturk et al., 2003). We found glandular atrophy in 6.2%, metaplasia in 2.8% of the *H. pylori* infected children.

It is shown that gastric cancer was 3-6 times more common in *H. pylori* infected cases. Although gastric carcinoma is extremely rare in children representing only 0.05% of all gastrointestinal malignancies, its incidence increases with age (Goldthorn et al., 1986). Recently a case of gastric adenocarcinoma presenting with gastric outlet obstruction in a child was reported by Al Hussaini (2014). In our group we did not encounter with malignancy development in any of our samples. The pathological changes in gastric mucosa that might thought to progress gastric cancer were mild and rare even in group of patients with family history of gastric cancer. It was also shown that mild to moderate glandular atrophy and/or intestinal metaplasia may be reversible after *H. pylori* eradication.

In adults gastric cancer ranks forth in incidence (after lung, breast and colorectal) and second in mortality (after lung cancer) among all cancers worldwide (Jemal et al., 2011). *H. pylori* was shown to cause oxidative stress induced apoptosis and DNA damage in gastric epithelial changes (Harbower et al., 2014). In an analysis of gastric tissues from mice and patients, Chaturvedi et al. (2014) identified the role of activation of phosphorylated epidermal growth factor receptor and erythroblastic leukemia-associated viral oncogene by *H. pylori* in the initiation of gastric carcinogenesis.

Its role in the development of gastric cancer is still obscure but the proposed mechanisms are induction of the bacterium induces a chronic inflammatory response, which is associated with epigenetic alterations in oncogenes, tumor-suppressor genes, cell-cycle regulators, and cell-adhesion molecules by the bacteria (Alvarez et al., 2013). Recently Guang et al. (2014) reported upregulation of mucin (MUC)1 mRNA in gastric cancer cells by *H. pylori*. In a study from Colombia patients from the area of high risk for gastric cancer were found to have significantly greater methylation levels of a tumor suppressor gene in the gastric mucosa. In addition, significantly elevated methylation levels were also found in patients infected with the virulent *H. pylori* strains (Schneider et al., 2010).

Gastric mucosal lesion caused *H. pylori* infection is

usually reversible process at the beginning. Early detection and eradication of bacteria resolves inflammation and restores the gastric mucosa. From this point of view early detection and eradication of *H. pylori* infection in children provides more effective prevention of gastric cancer since mucosal exposure time to carcinogen is relatively shorter, and mucosal pathologies are milder when compared to adults. If untreated bacteria persists for lifelong, it may lead to mucosal pathologies that might result in cancer. Early detection, effective eradication and prevention programmes may lead to a decrease in *H. pylori* incidence and gastritis especially in endemic areas. In a recent metaanalysis it was shown that there is an evidence that searching for and eradicating *H. pylori* reduces the incidence of gastric cancer in healthy asymptomatic infected people (Ford et al., 2014). It may be suggested that eradication of infection in children and follow up can lead to prevention of *H. pylori* associated malignant gastric disease up to 70-80% of cases in the future. Awareness about the *H. pylori* infection and its consequences is especially important for family members (adults and children) of gastric cancer patients.

One of the significant findings of this study was related with possible cancer prevention for *H. pylori* infected children. It was proven that the eradication of *H. pylori* infection improved the biopsy characteristics which may lead cancer. In this study, cases with gastric atrophy and glandular metaplasia had endoscopic evaluation one year later. No gastric atrophy and/or metaplasia was present in the control endoscopy.

The current study suggests a higher prevalence of familial history of gastric cancer in *H. pylori* infected children. Intestinal metaplasia was also higher in biopsy samples of *H. pylori* infected children. Determination and eradication of *H. pylori* infection for this risk group may prevent subsequent development of gastric cancer for these children as no gastric atrophy and/or metaplasia was seen in the control endoscopy.

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