Arch Pediatr Infect Dis. 2016 January; 4(1): e26639. doi: 10.5812/pedinfect.26639

Published online 2016 January 16. **Research Article**

Helicobacter pylori Seropositivity in Children With Asthma

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Received 2015 January 3; **Revised** 2015 November 2; **Accepted** 2015 November 14.

Abstract

Background: Some studies have reported an association between *Helicobacter pylori* (*H. pylori*) colonization and the occurrence of asthma or other allergies. However, data are inconsistent, and few studies have been performed in children.
Objectives: The current study aimed to investigate *H. pylori* seropositivity in children with and without asthma.
Patients and Methods: This cross-sectional study was performed with 208 children aged 5- to 12-years-old (104 asthmatic subjects in the case group and 104 healthy individuals in the control group) who had been referred to the pediatric clinic of Amir Kabir hospital in Arak, Iran. *H. pylori* seropositivity was compared between the two groups according to the serum level of immunoglobulin G (IgG) antibody against the *H. pylori* cytotoxin-associated gene A (CagA) protein, which was measured using the enzyme-linked immunosorbent assay (ELISA).
Results: The *H. pylori* serology test was positive in 13 (12.5%) asthmatic subjects and 18 (17.3%) healthy subjects. This difference was not significant (P = 0.54). Duration of asthma in the serology-positive children (3.61 ± 1.5 years) was significantly higher than that of the serology-negative children (2.16 ± 1.33 years) (P = 0.0001). No significant correlations were found between *H. pylori* seropositivity and age (P = 0.95), gender (P = 0.7), severity of asthma (P = 0.54), control of the asthma (P = 0.23), or pulmonary function test (PFT) results (P = 0.23).
Conclusions: The results showed no association between childhood asthma and *H. pylori* seropositivity. However, due to the lack of studies, especially in children, and controversial results of the clinical studies, further studies are recommended.

Keywords: Asthma, Child, *Helicobacter pylori*

1. Background

Asthma is a common chronic childhood disease, and it is one of the most common causes of hospitalization among children (1). Asthma is associated with genetic risk factors and predisposing environmental factors (1), which often begin during the early years of life (1).

Several factors, such as air pollution, exposure to cigarette smoke, external infections, microbial substances in the environment, ownership of furry pets, and obesity, play a role in the development of asthma (2). According to the hygiene hypothesis, people's reduced risk of and exposure to bacterial infections during childhood can cause atopic disorders, including asthma (3). Evidence suggests that early exposure to orofecal microbes, such as hepatitis A, can be a protective factor against allergic reactions (4). Moreover, according to this hypothesis, there is an inverse relationship of toxoplasma and *Helicobacter pylori* (*H. pylori*) with atopy (5).

H. pylori is a gram-negative bacterium that colonizes the stomach in more than half of the general population (6). It causes a variety of diseases, such as gastritis, peptic ulcer disease, gastric cancer, and lymphoid tissue lymphomas (7). It has recently been found that there is an inverse relationship between *H. pylori* and risk of gastroesophageal reflux disease (GERD) (8, 9). Given that there is a relationship between asthma and risk of GERD in some patients (10), this has led some authors to suggest that *H. pylori* might act as a protective factor against GERD-related asthma. In agreement with the hygiene hypothesis (3) and the notion of GERD-related asthma (10), an inverse association has been observed in some studies (10, 11) between *H. pylori* colonization and the occurrence of asthma or allergy.

2. Objectives

Since existing data are inconsistent and few studies have been performed in children (12), the aim of this study was to investigate *H. pylori* seropositivity in children with and without asthma.

3. Patients and Methods

During this cross-sectional study, which took place from November 2013 to May 2014, 104 five- to twelve-year-old children with documented asthma (for at least one year) were enrolled as a case group, and 104 age-matched healthy children were enrolled as a control group. All the subjects had been referred to our pediatric clinic of asthma and allergy and the general pediatric clinic of Amir Kabir hospital in Arak, Iran. Subjects who met the inclusion and exclusion criteria were selected based on simple probability.

Asthma was defined based on the 2008 global initiative for asthma (GINA) definition, as follows: asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitation (13).

Asthma is difficult to diagnose in infants and young children, for whom testing of reversible airway obstruction is technically difficult. Therefore, wheezing is often used as a proxy for asthma in children in epidemiological studies (6). In this study, for better evaluation of the asthma diagnosis, wheezing and current physician-diagnosed asthma are used as a proxy for asthma in children (6). Diagnosis of asthma was confirmed by a physician by asking the children's parents the following questions: 1) Has your child made a whistling noise while breathing in the last 12 months?; 2) Has your child ever been diagnosed with asthma by a physician?; 3) Has your child had asthma in the last 12 months?

Our exclusion criteria were: 1) an exacerbation of asthma in the preceding month for the case group; 2) history of peptic ulcer, cerebrovascular disease, ischemic heart disease, or respiratory diseases (except asthma in the case group); 3) documented *H. pylori* infection; 4) prior *H. pylori* eradication therapy; 5) consumption of acid-suppressive drugs (proton pump inhibitors (PPIs), H2 receptor antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), and antibiotics (such as amoxicillin, tetracycline, metronidazole, and clarithromycin; for at least 1 - 2 weeks)) in the preceding six months for gastric or other problems; 6) history of congenital gastrointestinal (GI) anomalies, gastric surgery, gastric malignancies, or any significant GI problem; 7) history of chronic diseases, especially autoimmune disorders; and 8) recent exposure to any infectious disease.

Following primary evaluation regarding the exclusion/inclusion criteria and receipt of informed consent from children's parents for participating in the study, the following information was recorded: baseline characteristics (age, gender, residence); clinical information of the asthmatic group (duration of asthma (years), severity and control status of the asthma, and pulmonary functional test (PFT) results). Severity of the asthma was classified as mild/intermittent or more severe. The PFT results were classified as normal or as indicative of obstructive disease. *H. pylori* seropositivity was defined as a positive result of the serum level of IgG antibody against the *H. pylori* surface cytotoxin-associated gene A (CagA) protein (14-16).

Peripheral venous blood was drawn from the children. The samples were centrifuged, and the serum isolated from them was placed at −20°C prior to the serological test. In order to check for the presence of IgG antibody against the *H. pylori* surface CagA protein, all sera were analyzed using the enzyme-linked immunosorbent assay (ELISA) (Binding Site, UK), and IgG was measured according to the manufacturer's protocol. When the concentration of IgG antibodies against *H. pylori* was greater than 20 U/mL or less than 12.5 U/mL, the result was considered positive or negative, respectively. The results of the antibody test were analyzed by a person unaware of the children's asthma status.

The collected data were analyzed using SPSS software (statistical package for the social sciences, version 18.0, SPSS Inc., Chicago, IL, USA) and descriptive statistics methods for frequency determination. Numerical data are expressed as the mean ± standard deviation (SD) and were compared using the t-test. Categorical data are expressed as numbers (percentages) and were compared with the chi-square test. P values less than .05 were considered significant. This study was approved by The ethics committee of Arak University of Medical Sciences. In all stages of this study we were loyal to the Helsinki declaration principles, and we obtained written consent from all the participants, who were free to exit the study at any time.

4. Results

The baseline characteristics of the 208 children selected for the study are shown in Table 1. The distributions of age (P = 0.32), gender (P = 0.37), and residence (P = 0.08) of the children were not significantly different between the two groups. The mean serum level of IgG against the CagA protein was 8.46 ± 2.47 U/mL and 12.74 ± 9.41 U/mL in the asthmatic and control groups, respectively. This difference was not significant (P = 0.23). IgG against the CagA protein was present in 31 (14.9%) of the 208 subjects in the two groups, which shows that there was no significant difference between the children with 13 (12.5%) and without 18 (17.3%) asthma (P = 0.54) (Table 2).

In the asthmatic group, the results of the *H. pylori* serology test were analyzed according to age, gender, severity and control status of the asthma, duration of the disease, and PFT results (Table 3). The duration of asthma in the serology-positive children (3.61 ± 1.5 years) was significantly higher than that of the serology-negative children (2.16 ± 1.33 years) (P = 0.0001). No significant correlations were found between *H. pylori* seropositivity and age (P = 0.95), gender (P = 0.7), severity of asthma (P = 0.54), controlled asthma (P = 0.23), or PFT results (P = 0.23).

Table 1. Baseline Characteristics of the Study Groups

Characteristic	Children With Asthma [a]	Healthy Children [a]	P Value [b]
Age, y [c]	7.23 ± 3.3	6.5 ± 3.84	0.32
Gender [d]			0.37
Male	34 (32.6)	40 (38.4)	
Female	70 (67.3)	64 (61.5)	
Residence [d]			0.08
Urban	74 (71.1)	69 (66.3)	
Rural	30 (28.8)	35 (33.6)	

[a]Number of subjects = 104.
[b]P values less than 0.05 were considered significant.
[c]Values are presented as mean ± SD.
[d]Values are presented as No. (%).

Table 2. Results of Serum Testing for IgG Antibody Against the *H. pylori* Surface CagA Protein in the Study Groups[a]

IgG Serology Test Result	Asthmatic Group [b]	Healthy Group [b]	P Value
Positive [c]	13 (12.5)	18 (17.3)	0.54
Negative [d]	91 (87.5)	86 (82.6)	0.54

[a]Values are presented as No. (%).
[b]Number of subjects = 104.
[c]IgG concentrations higher than 20 U/L.
[d]IgG concentrations less than 12.5 U/mL.

Table 3. *H. pylori* Serology Test Results Among Asthmatic Patients[a,b]

Characteristic	Serology-Positive (n = 13)	Serology-Negative (n = 91)	P Value
Age	7.38 ±1.75	7.35 ± 2.14	0.95
Gender			0.7
Male	7 (53.8)	54 (59.3)	
Female	6 (46.1)	37 (40.6)	
Duration of disease, y	3.61 ± 1.5	2.16 ± 1.33	0.0001
Control status of disease			0.23
Controlled	12 (92.3)	71 (78)	
Uncontrolled	1 (7.6)	20 (21.9)	
Severity of disease			0.54
Persistently mild	9 (69.2)	55 (60.4)	
Moderate and severe	4 (30.7)	36 (39.5)	
PFT			0.23
Normal result	12 (92.3)	71 (78)	
Obstructive disease	1 (7.6)	20 (21.9)	

[a]Abbreviations: PFT, pulmonary function test.
[b]Values are presented as No. (%) or mean ± SD.

5. Discussion

This study shows that there is no significant difference in *H. pylori* seropositivity between children with and without asthma. However, there was an association between prolonged duration of disease in asthmatic children and *H. pylori* seropositivity. In contrast to our findings, various cross-sectional and case-control studies have shown an inverse relationship of asthma and allergic rhinitis with *H. pylori* colonization, especially for CagA+ strains (10, 11, 17). Based on the third national health and nutrition examination survey (NHANES III) (18) database, Chen et al. (10) showed that there is an inverse relationship between seropositivity for CagA+ strains of *H. pylori* and risk

of asthma, especially in young people and those who suffered from asthma during childhood. Likewise, in a case-control study Reibman et al. (11) reported seropositivity for CagA+ strains of *H. pylori* in 47.1% of all study samples and showed that there is an inverse relationship between the risk of asthma and CagA seropositivity. Furthermore, Shiotani et al. (17) studied the prevalence of serum *H. pylori* IgG among 369 university students with a history of allergic diseases (allergic rhinoconjunctivitis, atopic dermatitis, urticaria, bronchial asthma, and mixed diseases) and 408 control subjects and found that the prevalence of *H. pylori* seropositivity in the allergic group was significantly lower than that of the control group.

However, similar to our study, a few studies have reported no association (19) or a weak inverse association (20) of *H. pylori* colonization with asthma and allergy. In a study by Jarvis et al. (19) in 2004, previous infection with hepatitis A or *H. pylori* was assessed in a community-based sample of young British adults, and associations of serum-specific IgE with environmental allergens, asthma-like symptoms, and hay fever were investigated. They found no evidence of a relationship between hepatitis A or *H. pylori* infection with lower levels of IgE sensitization, asthma, or hay fever. Furthermore, Tsang et al. (20) did not find any significant difference between people with and without asthma in terms of the presence of *H. pylori*-specific IgG. They also did not report any relationship between serum levels of IgG and forced expiratory volume in 1 second (FEV1 % predicted), forced vital capacity (FVC % predicted), or duration of asthma.

In a cross-sectional study by Karimi et al. (21) in Iran, *H. pylori* infection was compared between 98 asthmatic children and 98 healthy individuals. Unlike many studies, *H. pylori* infection was diagnosed using the urea breath test (UBT); nonetheless, UBT positivity was not significantly different between the asthmatic 18 (18.3%) and healthy 23 (23.3%) children. Furthermore, analysis of the asthmatic group revealed an association of *H. pylori* infection with age ($P < 0.001$) and duration of asthma ($P = 0.010$).

The hygiene hypothesis and the potential role of *H. pylori* in protecting against GERD-related asthma are among the hypotheses supporting an inverse relationship between asthma and *H. pylori* (3, 10). According to the hygiene hypothesis, microbial infections in early childhood might act as a protective factor against allergy and asthma (22). Although the mechanism of this hypothesis is not entirely clear, early stimulation of gut-associated lymphoid tissue by infectious microbes, may play a role, the gut being the initial location for mucosal immune maturation (23). The role of *H. pylori* in protecting against GERD-related asthma was proposed based on the following evidence: (1) Asthma can be a risk factor for GERD (24, 25), (2) GERD can play a role in stimulating asthma (24, 25), and (3) There might be an inverse relationship between *H. pylori* and GERD (8, 9). According to previous evidence, this hypothesis is important because GERD is often not examined due to being asymptomatic, especially in children (26, 27).

In contrast to the above hypotheses, some authors believe that *H. pylori* colonization of the gastric mucosa may stimulate the secretion of various proinflammatory substances, such as cytokines and acute phase proteins (28). Accordingly, a direct relationship was proposed between *H. pylori* and diseases characterized by inflammation, such as asthma. A study has reported have reported a higher prevalence of *H. pylori* compared to healthy individuals in chronic inflammatory diseases, such as rosacea, urticarial, and Henoch-Schonlein purpura (29). Tsang et al. (30) showed a higher prevalence of *H. pylori* seropositivity in patients with bronchiectasis (76%) when compared with healthy individuals. Similarly, we found an association between prolonged duration of disease in asthmatic children with a higher incidence of *H. pylori* seropositivity; however, we found no general association between childhood asthma and the *H. pylori* seropositivity.

One of the limitations of this study is that endoscopic biopsy was not used to diagnose *H. pylori*. According to some observations (15, 16), serology tests have variable sensitivity and specificity in diagnosing *H. pylori* in children. In some cases, the results of the serology test can be influenced by the duration of infection and the ability of the host to mount an immune response. Therefore, it was suggested that endoscopic biopsy be conducted for a more definite diagnosis of *H. pylori* infection. However, the serology test was used in the current study for the following reasons: (1) endoscopy is an invasive procedure, and there is no indication for this diagnostic method in the evaluation of children who do not have gastrointestinal symptoms; and (2) parents may have been unwilling for their child to undergo the procedure. Nevertheless, it is recommended that future studies be conducted using endoscopy to diagnose *H. pylori* in children with gastrointestinal symptoms so that more accurate results can be obtained.

Although many studies have been carried out on the relationship between asthma and *H. pylori* seropositivity and/or infection, further clinical and laboratory studies are recommended to be conducted in future due to (1) contradictory hypotheses on the relationship between *H. pylori* and asthma, (2) controversial results of the clinical studies, (3) lack of studies in children, and (4) lack of evidence in regard to the association between the clinical features of asthma and *H. pylori*.

Acknowledgments

The research team wishes to thank the vice chancellor of research for financial support and also the children and their parents who enabled this research.

Footnotes

Authors' Contribution: Parsa Yousefichaijan and Ghasem Mosayebi participated in the design of the study, performed the data collection, performed the statistical analysis, and served as the lead authors of the manuscript. Mojtaba Sharafkhah participated in the design

of the study, the statistical analysis, and in finalizing the manuscript. Manijeh Kahbazi, Phaezeh Heydarbagi wrote some parts of the draft. Mohammad Rafiei participated in the design of the study and the statistical analysis. All authors read and approved the final manuscript.

Funding/Support: This study was financially supported by Arak University of Medical Sciences.

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