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Evaluation of the Correlation Between Childhood Asthma and *Helicobacter pylori* in Kashan

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Background: Asthma is a chronic inflammatory air-way disease with increasing prevalence rate during the recent years. There are studies about the relationship between asthma and infectious diseases, including the association between asthma and *Helicobacter pylori*. According to the latest studies, there is an epidemiological correlation between asthma prevalence and prevalence of *H. pylori*.
Objectives: The aim of this research was to study the correlation between *H. pylori* and asthma by biopsy in five to eighteen year-old children who had undergone endoscopy at Shahid Beheshti Hospital.
Patients and Methods: Three hundred children (5 to 18 years old) undergoing endoscopy owing to gastro-intestinal problems at Shahid Beheshti Hospital were observed for childhood asthma using the Gina 2010 questionnaire which included 24 questions with "yes" and "no" answers to identify asthmatic patients with five positive answers. Next, the patients were referred to an allergy and asthma specialist for clinical examinations, spirometry and post bronchodilator test (Post BD).
Results: Among 138 *H. pylori* positive patients, eight cases (5.8 %) were asthmatic while of the 162 *H. pylori* negative patients 28 (17.3%) were asthmatic. This difference was statistically significant (P Value = 0.002). The correlation between *H. pylori* and asthma was studied after controlling the confounding variables including, gender, age and family history. The results obtained for the above-mentioned variables were significant (P Values of 0.004, 0.005 and 0.002, and Odd-Ratio Mantel Haenszel (ORMH) of 3.38, 3.24 and 4.06, respectively).
Conclusions: Our findings showed that there is an inverse correlation between *H. pylori* and asthma. Performing more studies with larger sample sizes is necessary to confirm these results.

Keywords: Helicobacter pylori; Asthma; Childhood Asthma

1. Background

Asthma is a chronic inflammatory disease which appears with edema and inflammation. It is mostly considered as a reversible stricture in airway tracts, which could be followed by some viral respiratory infections such as respiratory syncytial virus (RSV) in children. It may present symptoms such as wheezing, shortness of breath and coughing. Although, the exact cause of asthma has not been identified, yet a combination of environmental factors, biological genetic tendencies, inhaled allergens, viral infections, and chemical-biological pollutants such as tobacco play an important role in this respect. The immunological response could be a stimulant for chronic inflammation and inappropriate healing in damaged tissue of airway tracts. These pathological processes in growing-up lungs at an early age cause negative effects upon airway tracts' growth and evolution (1).

In the United States of America, childhood asthma is one of the most common reasons of reference to the emergency departments and hospitalization. Asthma was responsible for 12.8 million absent days of school in 2004, 750000 episodes of referring to urgency services, 198000 episodes of hospitalization and 186 episodes of death in children. It has been pointed out that a combination of biological, environmental, economical, and mental risk factors could increase the possibility of severe ablaze of asthma (2). During the last decades, it seems that prevalence of childhood asthma is increasing in spite of remarkable improvement in management and pharmacotherapy (3). Several published studies in different countries have reported a 50% increase in prevalence during the recent decade (4-7). It has been demonstrated that there is a correlation between asthma prevalence and allergic rhino conjunctivitis and atopic eczema (8).

It is assumed that childhood asthma is more common in modern capitals and crowded nations and correlates extremely with other allergic reactions (9). In compari-

son, there is less possibility for children who live in rural areas of developing countries to become asthmatic (10). In the recent years, many studies have been conducted to determine the correlation between allergic reactions and infectious diseases (11-14). *Helicobacter pylori* is a urease-positive Gram-negative microaerophilic bacteria that grows in the stomach's mucosa and stimulates the human immune system (15), which helps release bacteria and host's inflammatory mediators in the blood (16). Recent studies showed that *H. pylori* could cause chronic gastritis (3), peptic ulcer disease (PUD) (6) and stomach cancer (15). In addition, there is a direct correlation between *H. pylori* infection and B-Cell lymphoma (17), and cardiac, dermal, hepatic and rheumatologic diseases (18). It has been identified that *H. pylori* could produce pre-inflammatory mediators such as cytokines, eicosanoids and acute phase proteins in stomach mucosa, which can explain the correlation between *H. pylori* and inflammatory diseases (19) beside the similarity of antigens of the bacterium and the host (20).

2. Objectives

As the correlation between *H. pylori* and some inflammatory diseases has been proved in the recent years, this study was conducted to study the correlation between *H. pylori* infection and childhood asthma.

3. Patients and Methods

Three hundred children (5 to 18 years old) undergoing endoscopy owing to gastro-intestinal problems at Shahid Beheshti Hospital were observed for childhood asthma by the Gina 2010 questionnaire, which includes 24 questions with "yes" and "no" answers. The children were identified as asthmatic with five positive answers (21). Next, the patients were referred to an allergy and asthma specialist for clinical examinations, spirometry, and also post bronchodilator test (Post BD). Finally, results of the questionnaires, clinical examinations, spirometric findings, and pathological reports were analyzed by the SPSS version 16.0 software, via Fisher and chi square tests.

4. Results

The youngest examined child was five years old while the oldest was 18 years old. One hundred and forty-three children (47.7%) were male and 157 (52.3 %) were female. The mean age was 11.17 ± 4.03. Children with *H. pylori* had a mean age of 11.73 ± 4.3 while those without this infection had a mean age of 10.95 ± 3.78; no significant difference was observed (P = 0.312). The mean age of children with asthma was 11.23 ± 4.07 while the mean age of those without asthma was 10.72 ± 3.7, no significant difference was indicated (P = 0.481). The Mann Whitney U test was used to compare the mean age of children. Forty-three of the cases (14.3%) had an asthmatic family history. Amongst the 138 *H. pylori* positive patients, eight cases (5.8 %) were asthmatic while of the 162 *H. pylori* negative patients 28 cases (17.3%) were asthmatic, with the difference being statistically significant (P Value = 0.002) (Table 1). The spirometric findings considered as mild, moderate and severe stages in obstruction of lower-respiratory tracts were consistent with the questionnaire; all cases of disease were confirmed by an Asthma and Allergy specialist.

The correlation between *H. pylori* and asthma was studied after controlling for confounding variables, including gender, age, and family history. The obtained results for the above-mentioned variables were significant (P values of 0.004, 0.005 and 0.002, respectively) (Tables 2, 3 and 4). Also, the Odd-Ratio Mantel Haenszel (ORMH) of all of the three comparisons were obtained ($ORMH_{gender} = 3.38$, $ORMH_{age} = 3.24$ and $ORMH_{familial\ history} = 4.06$).

Table 1. Frequency of Distribution of Asthma in the Two Groups of *H. pylori* Positive and Negative Children [a,b]

Asthma	*H. pylori* (Positive)	*H. pylori* (Negative)	*H. pylori* (Total)
Positive	8 (5.8)	28 (17.3)	36 (12)
Negative	130 (94.2)	134 (82.7)	364 (88)
Total	138 (100)	162 (100)	300 (100)

[a] P Value = 0.002; OR 1 = 3.39; CI 2 = 1.49 - 7.7.
[b] Data are presented as No. (%).

Table 2. Frequency of Distribution of Children According to Gender and the Situation of *Helicobacter pylori* and Asthma [a,b]

Asthma	*H. pylori* (Positive)	*H. pylori* (Negative)	*H. pylori* (Total)
Male			
Positive	3 (4.5)	13 (17.1)	16 (11.2)
Negative	64 (95.5)	63 (82.9)	127 (88.8)
Total	67 (100)	76 (100)	143 (100)
Female			
Positive	5 (7)	15 (17.4)	20 (12.7)
Negative	66 (93)	71 (82.6)	137 (87.3)
Total	71 (100)	86 (100)	157 (100)

[a] P Value = 0.004 (Mental-Haenszel); OR = 3.38; CI = 1.2 - 7.6.
[b] Data are presented as No. (%).

Table 3. Frequency of Distribution of Children According to Age and the Situation Of *Helicobacter pylori* and Asthma [a,b]

Asthma	*H. pylori* (Positive)	*H. pylori* (Negative)	*H. pylori* (Total)
≤ 12, y			
Positive	4 (3.5)	21 (16.7)	25 (10.4)
Negative	110 (96.5)	105 (83.3)	215 (89.6)
Total	114 (100)	126 (100)	240 (100)
> 12, y			
Positive	4 (83.3)	7 (19.4)	11 (18.3)
Negative	20 (83.3)	29 (80.6)	49 (81.7)
Total	24 (100)	36 (100)	60 (100)

[a] P Value = 0.005 (Mental-Haenszel); OR = 3.24; CI = 1.4 - 7.37.
[b] Data are presented as No. (%).

Table 4. Frequency of Distribution of Children According to Family History and the Situation of *Helicobacter pylori* and Asthma [a,b]

Asthma (Family History Regarding of Asthma)	*H. pylori* (Positive)	*H. pylori* (Negative)	*H. pylori* (Total)
Positive			
Positive	4 (16.7)	7 (36.8)	11 (25.6)
Negative	20 (83.3)	12 (63.2)	32 (74.4)
Total	24 (100)	19 (100)	43 (100)
Negative			
Positive	4 (3.5)	21 (14.7)	25 (9.7)
Negative	110 (96.5)	122 (85.3)	232 (90.3)
Total	114 (100)	143 (100)	257 (100)

[a] P Value = 0.002 (Mental-Haenszel); OR = 4.06; CI = 1.7 - 9.6.
[b] Data are presented as No. (%).

5. Discussion

Among the 300 children under study, 36 (12 %) were asthmatic and 138 (46 %) were infected by *H. pylori*. The prevalence of the asthma has increased across the world for all ages, both genders, and all races from 7.3 to 8.2% during years 2001 to 2009 (8, 4). Also, in 2011, 14% of children under 17 years of age had been described as asthmatic (22). Nowadays, attention is being paid to exogenous contacts with environmental microorganisms and their anti-genes, which are able to make harmful changes in the human immune system (11). Hygiene hypothesis is a hypothesis, which states that a lack of early childhood exposure to infectious agents, symbiotic microorganisms (e.g. gut flora or probiotics), and parasites increases susceptibility to allergic diseases by suppressing the natural development of the immune system causing change in the TH1/TH2 ratio, which leads to an increase in allergic disorders (21).

It is believed that asthma could appear due to uncontrolled immunological response to environmental antigenes by TH2 cells. Overcoming the number of TH2 to TH1 cells resulting from less contact with environmental microorganisms causes development of asthma. According to D'Elios and Bernard, lack of TH1 cells stimulation causes hyper-activity in TH2 cells, which could lead to asthma (7). The *H. pylori* is a urease-positive gram-negative microaerophilic bacteria in the stomach that has spread in most populations. The *H. pylori* remains in the mucosal layer of the stomach for decades and people under the age of ten could become infected and transfer the infection to other family members as well (14). The antibody response following *H. pylori* infection would remain stably with *H. pyloric* gastric colonization for decades or for an entire lifetime. It has been determined that colonization of *H. pylori* in the mucosal layer of the stomach would increase different pre-inflammatory mediators such as cytokines and acute phase proteins (23). Therefore, there is a pathogenic correlation between *H. pylori* infection and the diseases, which would appear by action of inflammatory mediators and/or auto-immune induction (12). *Helicobacter pylori* infection decreases TH2 cells leading to a reduction of TH1 cells number (24). It can also decrease the prevalence of severe allergic responses by induction of regulatory T cells (2, 25).

In the current study, 138 cases (46%) out of 300 were *H. pylori* positive as illustrated by their biopsy samples. Several

studies have been performed on the correlation of oral-fecal infections and asthma with controversial results. *Helicobacter pylori* has been introduced as an allergy stimulant by some researches (26), while others claim that it has a protective role against allergies (27) and a number of studies suggest its miscorrelation with allergic diseases (13). Among the 138 *H. pylori* positive patients, eight cases (5.8 %) and among the 162 *H. pylori* negative, 28 cases (17.3 %) were asthmatic, showing a statistic difference with odds ratio of 3.39. The obtained results are compatible with several other studies in which an inverse correlation between *H. pylori* anti-bodies and asthma has been revealed. For instance, results obtained by Arram et al. pointed out that there is a significant difference in *H. pylori* infection in asthmatic patients compared with the control group (9). The study of Chen and Blaser indicated that *H. pylori* infection could significantly reduce the risk of asthma and emphasized that performing more researches in order to orientate the exact mechanisms of action are necessary (5).

Study of Zevit et al. on 6959 children indicated that there is an inverse correlation between childhood asthma and *H. pylori* infection (28). However, Tsang et al. (29) and Jaber (30) showed that there is no correlation between *H. pylori* infection and asthma. There is little evidence on the inverse correlation between *H. pylori* and asthma as indicated by Wang et al. (31). Fullerton et al. in a study performed on 2437 patients showed that there is no correlation between *H. pylori* serology and pulmonary function tests (10). The diagnostic method of *H. pylori* has been different in previous studies. Some used *H. pylori* serology tests in which sensitivity and specificity related to variables play an important role (50 to 100 %); and this could be a strong confounding factor and also a justification for the obtained incommensurable results in the above-mentioned researches. On the other hand, some factors such as gender, age, and family history of asthma could be considered as strong confounding factors, which affect *H. pylori* and asthma leading to incommensurable results.

The advantage of the present study is that some features such as age, gender, and family history were considered in the assessment of patients and that diagnosis of *H. pylori* infection was made by the biopsy method, which has a higher sensitivity and specificity than serology tests. There is an inverse correlation between *H. pylori* and asthma as indicated by our findings. Performing more studies with larger sample sizes is necessary to confirm these results. Obviously, precise recognition of the correlation between *H. pylori* infection and asthma could play an important role in the recognition of the physiopathology of not only asthma but also other allergic diseases, which would offer potentially helpful new treatments for allergic diseases.

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