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Allergic asthma is inversely associated with *Helicobacter pylori* seropositivity

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Abstract:

Background: Allergic asthma is a chronic inflammatory disease where the airways are characterized by hyper-responsiveness to certain allergens, mucus hyper-secretion and eosinophilic infiltration. These events are believed to be the inevitable outcome of imbalance between type 1 T helper (Th1) cells and type 2 T helper (Th2) cells responses. In asthma, exposure to specific allergens can elicit the release of allergic cytokines through upregulation of Th2 cells mediated pathway. Based on hygiene hypothesis, it is believed that exposure to exogenous pathogens can reduce asthma prevalence by shifting immune system balance toward domination of Th1 cells mediated response. In this trend, several studies have shown that *Helicobacter pylori* (H. pylori) infection can reduce prevalence of allergic asthma. This gram negative bacterium can amplify Th1 immune response through multiple mechanisms.

Objective: The aim of this screening study is to explore any potential link between allergic asthma prevalence and H. pylori infection.

Methods: In this case-control study, we screened 30 asthmatic and 30 non-asthmatic volunteers for H. pylori IgG antibodies by immunohistochemical approach.

Results: the seropositivity of *Helicobacter pylori* IgG antibodies was significantly higher in non-asthmatic group (67%) than in asthmatic patients (37%); (P value = 0.009; Odds ratio = 5.50; confidence interval = 1.54-19.63).

Conclusions: Our findings significantly indicate that H. pylori infection is inversely associated with allergic asthma; it is also evident that absence of H. pylori infection can increase asthma risk by more than five times. Such possible association may be employed in future to design asthma preventive remedy by using H. pylori derived products.

Keywords: Allergic asthma, *Helicobacter pylori*, association, case-control, T helper cells.

INTRODUCTION:

Allergic asthma is a chronic multifactorial disease of the airway passages that can be developed at any age. It is characterized by eosinophilic inflammation of airways, shortness of breath, wheezing and coughing. Asthma is a significant public health problem that can adversely impact the quality of life (1).

Allergic asthma is mainly caused by overactive type 2 T helper (Th2) cells mediated immune response and diminished type 1 T helper (Th1) cellular activity. Upon exposure to specific allergen, excessive production of allergic cytokines (IL-4, IL-5, and IL-13) will lead to release of IgE by B lymphocytes and infiltration of eosinophils (2-4).

Based on epidemiological studies and the hygiene hypothesis, infectious diseases can influence the course of various allergic conditions by modifying Th1/ Th2 responses balance. Exogenous pathogens like bacteria can induce the release of IL-12, TNF-α, and INF-γ by Th1 cells. This can inhibit any allergic reaction through domination of Th1 immune mediated response over Th2 allergic pathway (5-8).

Several studies have proposed an association between *Helicobacter pylori* (H. pylori) infection and reduced incidence of allergic asthma (9-11). H. pylori is a gram negative bacterium, it is considered a well-known risk factor for developing peptic ulcer, gastric cancer and gastric lymphoma (12-14). H. pylori may also contribute to the development of other diseases outside GIT like bronchitis and lung cancer (15).

H. pylori express several immunomodulatory proteins that can shift host's immunologic activity toward Th1 response. Of these, H. pylori neutrophil-activating protein (HP-NAP) has been found to induce the release of IL-12 and IFN-γ when administered systemically (16-18). Therefore, HP-NAP can be utilized for the development of a potential preventive approach against allergic asthma (9, 19).

Infection with H. pylori can cause atrophic gastritis; the reduction in acid content of stomach can minimize the risk of asthmatic attack. Atrophic gastritis is usually associated with increase in the level of gastrin; the latter can be accompanied by upregulated Th1 immune mediated pathway (20). The reduction in acid secretion can lower the risk of gastroesophageal reflux disease GERD, previous studies suggest that asthma attacks can be triggered by GERD (21).

In the current case-control study, we screened a group of asthmatic and non-asthmatic individuals for H. pylori IgG seropositivity. Our aim is to evaluate any possible link between allergic asthma risk and H. pylori infection.

MATERIALS AND METHODS:

Study samples:

For this study, 60 individuals were recruited voluntarily from Al-Hussain Teaching Hospital in Karbala province and Al-Sader General Teaching Hospital in Al-Najaf province (Iraq). The study was carried out between February and May 2018.

Of these volunteers, 30 patients with a confirmed diagnosis of allergic asthma were included as a case group. The remaining 30 individuals (non-asthmatic) were used as a

control group. The employed protocol for this study is in compliance with the Iraqi board for medical specializations guideline. A verbal consent was obtained from each participant, demographic and clinical information were also collected from each individual. Any volunteer with a previous history of *Helicobacter pylori* eradication course was excluded from the study.

Serology test:

Anti-H. pylori IgG antibodies were assessed by using Accutest H. pylori whole blood cassette test (Catalog # ID392). For each volunteer, a whole blood fingerstick sampling was employed and one drop of blood was applied directly to the cassette well. After 30 seconds, about three drops of washing buffer were added to the well. The results were observed after 2-3 minutes, where one line (control line) indicates negative result while two lines (test and control lines) indicate presence of H. pylori IgG. The results were neglected and considered invalid when no line is ever detected or only test line is developed.

Statistical analysis:

The continuous variables were reported as mean ± standard deviation, the differences between control and case groups were evaluated by using unpaired t-test. Welch's correction was applied to overcome unequal variances.

For categorical variables, data were reported as frequencies (percentages). Chi-square test (χ^2) was used to compare case and control groups. Fisher's exact test was employed as an alternative to chi-square test for categorical samples with small size.

GraphPad prism version 5.01 was used for the analysis of the above data. To assess the risk of allergic asthma associated with the absence of H. pylori IgG, logistic regression was employed by using IBM SPSS Statistics version 20. For all these analysis, a two tailed P value less than 0.05 was considered statistically significant.

RESULTS:

Both case (asthma) and control groups were compared regarding demographic and clinical characteristics as seen in table 1. No significant difference was reported between these two groups in terms of body mass index (BMI), smoking habit, other concomitant diseases or family history of asthma. No occupational risk factors were ever reported for asthma and control groups.

From table 1, we can observe that asthmatic patients were significantly older than control patients (P value for age difference = 0.03). Gender distribution was remarkably different as more male volunteers were recruited for control group (76.67%) when compared to asthmatic patients (46.67%); (P value for gender distribution difference = 0.017).

Our association study between the incidence of asthma and *Helicobacter pylori* seropositivity is illustrated in table 2. According to regression analysis, the prevalence of H. pylori IgG antibodies was more common among control patients (67%) as compared to asthmatic ones (37%); (P value = 0.009; Odds ratio = 5.50; confidence interval = 1.54-19.63).

Table 1: Clinical and demographic characteristics.

Variable	Control Mean ± SD or N (%)	Case (Asthmatic) Mean ± SD or N (%)	P value
Age (years)	32.27 ± 14.37	41.33 ± 17.17	0.03
Gender: - Male - Female	 23 (76.67%) 07 (23.33%)	 14 (46.67%) 16 (53.33%)	0.017
BMI Kg/m^2	26 ± 6.61	28.47 ± 4.85	0.10 (NS)
Smokers	8 (26.67%)	7 (23.33%)	0.76 (NS)
Concomitant diseases: - Hypertension - Diabetes mellitus	 0 (0.00%) 2 (6.67%)	 3 (10.00%) 4 (13.33%)	0.24 (NS) 0.67 (NS)
Occupational risk factors	-	-	-
Family history	2 (6.67%)	6 (20%)	0.129 (NS)

SD: Standard deviation; **N:** Frequency; **BMI:** Body mass index; **NS:** Not significant.

Table 2: Prevalence of *Helicobacter pylori* antibodies among Asthmatic and control patients.

Prevalence of HP IgG	Control N (%)	Asthmatic N (%)	Total	P value*	Odds ratio (95% CI)
Positive	20 (67%)	11 (37%)	31 (52%)	0.009	5.50 (1.54-19.63)
Negative	10 (33%)	19 (63%)	29 (48%)		
Total	30 (100%)	30 (100%)	60 (100%)		

HP: *Helicobacter pylori*; **N:** Frequency; **95% CI:** 95% confidence interval.

*P value was adjusted for both age and gender.

DISCUSSION:

Allergic asthma attack is the definitive consequence of improper immune system functioning where exposure to specific allergens can elicit the release of IL-4, IL-5, and IL-13 through exaggerated Th2 response (1). Behind the scene, these cytokines can be considered as the main players to evoke pathological changes commonly seen in asthma. Switching of plasma cells to release IgE is mainly mediated by IL-4 (22), while IL-5 and IL-13 are essential for eosinophilic infiltration and mucus secretion respectively (23, 24).

Interestingly, exogenous pathogens can impede Th2 allergic pathway by shifting immune system toward Th1 response domination (5, 6). *Helicobacter pylori* is an exogenous bacterium that possesses several antigens and approaches to manipulate Th1/ Th2 responses balance and restrict asthma attack (1). In this trend, several studies had suggested an inverse association between prevalence of allergic asthma and H. pylori infection (9, 10).

In the current study, we excluded any volunteer with a previous history of H. pylori eradication therapy, as the employed screening technique is immunochromatography. The eradication therapy can eliminate H. pylori but the corresponding IgG antibodies can remain in circulation for

a long period afterward and this can adversely affect our screening results (25).

Our screening analysis refers to significant inverse association between prevalence of allergic asthma and *Helicobacter pylori* infection (P value = 0.009). Based on our results, it is well obvious that absence of H. pylori IgG antibodies can increase the risk of allergic asthma by more than five times (Odds ratio = 5.5). These findings fall in agreement with several previous case-control studies (26). Our samples were collected from developing community where the incidence rate of H. pylori infection is expected to be higher than in western countries, this can explain the more pronounced association observed in our analysis between H. pylori infection and asthma prevalence.

Further analysis of other samples may be required to elaborate the current potential relationship between *Helicobacter pylori* infection and allergic asthma prevalence as some previous studies failed to report any significant link between these two variables (27).

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