



Helicobacter pylori in allergic and non-allergic rhinitis does play a protective or causative role?

Umur Akiner¹ · H. Murat Yener² · E. Deniz Gozen² · S. Burcu Kuzu³ · Salih Canakcioglu²

Received: 16 July 2019 / Accepted: 14 September 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose Many studies have investigated the effect of *Helicobacter pylori* (*H. pylori*) colonization on the development of allergic diseases, but with conflicting results. The purpose of this cross-sectional observation study is to estimate *H. pylori* prevalence in allergic and nonallergic nasal conditions and compare with normal population.

Methods 274 patients were tested for *H. pylori* with stool antigen test. Patients were compared with the control group for *H. pylori* positivity rates after they were categorized according to their primary diagnoses as mite allergy, pollen allergy, mite and pollen allergy, and non-allergic rhinitis with eosinophilic syndrome (NARES). Results were also classified according to age.

Results The number of *H. pylori*-positive patients with mite allergy, mite and pollen allergy, and NARES were significantly higher than the control group in adults. The percentages of patients in the pediatric group who had mite allergy, pollen allergy, mite and pollen allergy, or NARES were not significantly different when compared to the control group.

Conclusion Forthcoming studies would undoubtedly evaluate of the profits of treating allergic nasal conditions by treating the aforementioned bacterial infection.

Keywords Rhinitis, Allergic · *Helicobacter pylori* · Rhinitis · Eosinophils · Rhinitis, Allergic, Seasonal · Rhinitis, Allergic, Perennial · Prevalence · Epidemiology · Cross-sectional studies · Hygiene hypothesis

Introduction

Over the past 50 years, allergies have become increasingly prevalent, especially in developed countries [1]. Some investigators believe that early childhood infections might play a protective role in the development of atopy [2], a hygiene theory that is supported by some studies, which have found that airborne infections, tuberculosis, and measles, for example, may play a protective role in atopy development [3–5]. Although single foodborne or orofecally transmitted infections have been shown to have a counter-ratio with regards to atopy and respiratory allergy prevalence [6–9], results in this field are still inconsistent [10].

Helicobacter pylori (*H. pylori*) is a common bacteria that colonizes in the gastric mucosa. Many studies have investigated the effect of *H. pylori* colonization on the development of allergic diseases, but with conflicting results [8, 9, 11–16]. To further investigate the association between the two, we investigated whether *H. pylori* colonization plays a role in allergic rhinitis and non-allergic rhinitis with eosinophilic syndrome (NARES).

Materials and methods

This cross-sectional observation study was designed by the Allergy Unit of Istanbul University's Cerrahpasa Medical School Otorhinolaryngology Department between January 2012 and January 2016; the institutional ethics committee (Istanbul University Cerrahpasa Medical School Institutional Review Board) approved the study protocol and all participants gave written informed consent.

Patients with allergic symptoms such as nasal obstruction, sneezing, and nasal discharge were enrolled in the study and evaluated by skin prick tests (SPT) (Soluprick ALK,

✉ Umur Akiner
umurakiner@gmail.com

¹ Otorhinolaryngology Department, Acibadem University Atakent Hospital, Istanbul, Turkey

² Otorhinolaryngology Department, Istanbul University Cerrahpasa Medical School, Istanbul, Turkey

³ Otorhinolaryngology Clinic, Amasya Merzifon Public Hospital, Amasya, Turkey

Denmark), nasal smears, and eosinophil cationic protein (ECP) blood tests. The SPTs consisted of 24 allergens, histamine, and a negative control panel, and were administered on the flexor aspect of the patient's forearm. The allergens tested included *D. pteronyssinus*, *D. farinea*, grass mix, tree mix, wool, cow's milk, hen's egg, cacao, dog epithelium, cat pelt, and mixed feathers. Reactions were measured after 15 min and the test results were considered positive if the wheal was larger than 5 mm or covered an area equivalent to at least 50% of a reference histamine reaction (1 mg/ml histamine chloride). Patients with positive skin tests were also evaluated with specific IgE blood tests. A diagnosis of allergic rhinitis was made in patients with both a positive skin prick test and a quantity of specific IgE greater than class 2.

Nasal smears were obtained by instructing the patients to blow their noses into wax paper then collecting and transferring these secretions to glass slides, staining them with Gram stain, and examining them under light microscope. A smear was considered positive for eosinophilia if more than 10% of the total leukocytes were eosinophils.

ECP in serum was determined using a double-antibody radioimmunoassay technique (Pharmacia CAP, Uppsala, Sweden). Blood samples were collected from venous vessels and were stored at -25°C until ECP measurements were taken. If nasal eosinophils accounted for more than 10% of the cells in the nasal smears or the ECP values were more than $15\text{ }\mu\text{g/l}$, this represented a diagnosis of NARES.

According to allergy and blood testing, 274 patients (170 female, 104 male; ages ranged from 3 to 76, with a mean of 30.68 ± 14.68 years) were diagnosed as having a pollen allergy, mite allergy or NARES were included in the study.

The control group for the study included patients without nasal complaints who had *H. pylori* stool antigen tests with the diagnosis of gastroesophageal reflux disease (GERD). *H. pylori* stool antigen tests have been performed to patients who have complaints compatible with the GERD in our clinics who are suitable for control group confirmed by previous studies. Recent systematic reviews also stated that the diagnosis of GERD was not affecting the *H. pylori* positivity [17].

The ages of the patients in the control group ranged from 4 to 76 years, with a mean average age of 27 ± 18.24 years. None of the patients in the study and control groups had previously been treated for *H. pylori* or allergic or non-allergic eosinophilic rhinitis. None of the patients in study and control groups had been tested for *H. pylori* before the onset of this study.

All the patients with allergic rhinitis or NARES, as well as the control group, were tested for *H. pylori* using a stool antigen test with HpSA EIA (*H. pylori* stool antigen enzyme immunoassay) (HpSA premier Platinum, Meridian Diagnostics, Cincinnati, OH) that detects *H. pylori* antigens

qualitatively. Patients who used antibiotics or medicines containing bismuth for 1 month before the test or proton pump inhibitors for 2 weeks before the test were excluded from the study.

The study and the control groups were also classified according to age, with analyses being performed for both pediatric patients (0–14 years old) and adults (over 14 years old). After patients had been categorized according to their primary diagnoses (mite allergy, pollen allergy, mite and pollen allergy, NARES), their sociodemographic data and *H. pylori* positivity rates were compared with those of the control group. SPSS v.16 for Windows, Chi-square, and *t*-test analyses were used for comparison.

Results

The study group included 274 patients in total (M: 104, F: 170; aged between 3–76; average age 30.68 ± 14.68), while the control group included 75 patients (M: 31, F: 44; aged between 4–76; average age 27 ± 18.24). The differences in these groups' gender and age distribution were not statistically significant. The adult study group included 227 patients (M: 79, F: 148; aged between 15–76; average age 35.04 ± 12.15) and the adult control group included 50 patients (M: 18, F: 32; aged between 15–76; average age 35.98 ± 15.82). The pediatric study group included 47 patients (M: 25, F: 22; aged between 3–14; average age 9.61 ± 2.64) and the pediatric control group included 25 patients (M: 13, F: 12; aged between 4–14; average age 9.04 ± 3.29). A comparison of sociodemographic data between study groups and the corresponding control groups revealed no statistically significant differences (see Table 1).

One hundred sixteen of 274 (42.3%) patients in the study group and 18 of 75 (24%) in the control group had positive *H. pylori* tests; the number of *H. pylori*-positive patients was significantly higher in the study group ($p=0.02$). One hundred five of 227 (46.2%) patients in the adult study group and 12 of 50 (24%) in the adult control group had positive *H. pylori* tests; again, the number of *H. pylori*-positive patients was significantly higher in the study group ($p=0.02$). In the pediatric group, 11 of 47 (23.4%) patients in the study group and 6 of 25 (24%) in the control group had positive *H. pylori* tests; however, there was no statistically significant difference between these two groups ($p=0.95$) (see Table 1).

Patients in the study group were categorized according to their diagnoses—mite allergy, pollen allergy, mite and pollen allergy, or NARES—and their age distribution. In the adult group, positive *H. pylori* tests were found in 40 of 95 (42.1%) patients with a mite allergy; 14 of 29 (48.2%) patients with a pollen allergy; 7 of 11 (63.6%) patients with a mite and pollen allergy; and 58 of 114 (50.8%) patients with NARES. The numbers of *H. pylori*-positive patients with a

Table 1 Comparison of the socio-demographical datas and *H. Pylori* positivity rates of study and control groups in different age ranges

	Study	Control	<i>p</i>
Adult			
Age	15–76; 35.04 ± 12.15	15–76; 35.98 ± 15.82	0.69
Gender	M: 79, F: 148	M: 18, F: 32	0.87
<i>H. pylori</i> positivity	105/227	12/50	0.02
Pediatric			
Age	3–14; 9.61 ± 2.64	4–14; 9.04 ± 3.29	0.45
Gender	M: 25, F: 22	M: 13, F: 12	0.82
<i>H. pylori</i> positivity	11/47	6/25	0.95
Total			
Age	3–76; 30.68 ± 14.68	4–76; 27 ± 18.24	0.11
Gender	M: 104, F: 170	M: 31, F: 44	0.46
<i>H. pylori</i> positivity	116/274	18/75	0.02

Bold values indicate statistically significant

mite allergy ($p=0.03$), mite and pollen allergy ($p=0.01$), and NARES ($p=0.001$) were significantly higher than in the control group (12 of 50 subjects, or 24%). Although the positivity rate of patients with a pollen allergy was higher than that of patients with a mite allergy (48.2% and 42.1% respectively), the difference was not significant when comparing patients with a pollen allergy to the control group (see Table 2).

The percentages of patients in the pediatric group who had mite allergy, pollen allergy, mite and pollen allergy, or NARES and a positive *H. pylori* test were 30.4%, 0%, 0%, and 18.1%, respectively. The differences were not significant when compared to the control group (24%) (see Table 2).

In the study group as a whole, the *H. pylori* positivity rates of patients with mite allergy, pollen allergy, mite and pollen allergy, and NARES were: 37.3% (47 of 118); 42.4% (14 of 33); 53.8% (7 of 13), and 45.5% (62 of 136), respectively. *H. pylori* positivity was 16% in the control group (12 of 75), and significant differences were found between the control group and the patients with a mite allergy ($p=0.02$), mite and pollen allergy ($p=0.029$), and NARES ($p=0.02$). Although the the rate of *H. pylori* positivity was higher in the pollen group, the difference was not statistically significant ($p=0.07$) (see Table 2).

Discussion

Recent studies indicate that allergic disease is becoming increasingly prevalent in developing countries, with even higher but more stable rates in developed countries [18].

Table 2 *H. pylori* positivity rates in different diagnosis and comparison to their corresponding control groups

Number of the individuals	<i>H. pylori</i> positivity (number/rate)	Sign. (<i>p</i>)
Adult group		
Mite allergy		
Study group ($n=95$)	40/42.1%	0.03
Control group ($n=50$)	12/24%	
Pollen allergy		
Study group ($n=29$)	14/48.2%	0.27
Control group ($n=50$)	12/24%	
NARES		
Study group ($n=114$)	58/50.8%	0.001
Control group ($n=50$)	12/24%	
Mite and pollen allergy together		
Study group ($n=11$)	7/63.6%	0.01
Control group ($n=50$)	12/24%	
Pediatric group		
Mite allergy		
Study group ($n=23$)	7/30.4%	0.62
Control group ($n=25$)	6/24%	
Pollen allergy		
Study group ($n=4$)	0/0%	0.28
Control group ($n=25$)	6/24%	
NARES		
Study group ($n=22$)	4/18.1%	0.63
Control group ($n=25$)	6/24%	
Mite and pollen allergy together		
Study group ($n=2$)	0/0%	0.62
Control group ($n=25$)	6/24%	
Total (adult + pediatric)		
Mite allergy		
Study group ($n=118$)	47/37.3%	0.02
Control group ($n=75$)	12/16%	
Pollen allergy		
Study group ($n=33$)	14/42.4%	0.07
Control group ($n=75$)	12/16%	
NARES		
Study group (136)	62/45.5%	0.02
Control group (75)	12/16%	
Mite and pollen allergy together		
Study group ($n=13$)	7/53.8%	0.029
Control group ($n=75$)	12/16%	

Bold values indicate statistically significant

Some studies explained this variation by suggesting that improved hygiene caused a reduction in microbial contact in the early stages of life and in turn resulted in higher prevalence of allergies later in life [19]. This role was explained by the “hygiene hypothesis”, which states that inadequate early exposure to microbial infections may suspend gut-associated lymphoid tissue stimulation [20].

The association between *H. pylori* infection and allergic conditions has been investigated in several studies. Matricardi et al. conducted one of the first such studies and they found that there was an inverse relation between *H. pylori*, Hepatitis A, and *Toxoplasma gondii* seropositivity and the prevalence of atopic disorders, but that there was no detectable relation between atopic diseases and airborne infections (measles, mumps, rubella, chickenpox, cytomegalovirus) [21]. The inverse relationship between *H. pylori* colonization and the prevalence of asthma and food allergies was demonstrated in some other studies [22, 23]. Chen et al. specified that childhood acquisition of *H. pylori* was associated with reduced risks of asthma and allergy [22]. Imamura et al. found similar results in pollinosis effects, especially in young study volunteers [24]. Janson et al. detected that the prevalence of positive serology in nonatopic subjects for *H. pylori*, herpes simplex virus 1, chlamydia pneumoniae, and cytomegalovirus was more frequent [25].

However, other investigations have refuted the relationship between *H. pylori* and allergic disorders. Uter et al. found a reverse association between allergic rhinitis and hepatitis B vaccination. However, the same study revealed no relationship between allergic rhinitis, hepatitis A, herpes simplex virus infection, and *H. pylori* infection [11]. Another study published in 2003 found a 30% reduction in the prevalence of atopic disorders such as allergic rhinitis, eczema, and asthma in people who had active *H. pylori* infection. The main limitation of this study, however, was that it included inadequate patient numbers for interpreting the significance of each individual atopic disorder, so it was unable to detect the effect of *H. pylori* on allergic rhinitis alone [8]. In this regard we only evaluated patients with allergic nasal conditions and we believe that this point improves our results.

The relation between *H. pylori* infection and allergic conditions quite controversial. Jarvis et al. detected no association between *H. pylori* infection and IgE sensitization, asthma, or hay fever [12]. Holster et al. detected no association between *H. pylori* serum-antibody status and allergic rhinitis, atopic dermatitis, or asthma [13].

Lately, Ma et al. mentioned that an inverse relationship between *H. pylori* and food allergies remains unproven due to the contradictory and limited nature of the evidence available to date. Nevertheless, they stated that in vitro evidence supports the notion that *H. pylori* can play a role in causing food allergies [14]. This was one of the first studies compatible with our results that indicate that there may be an association between *H. pylori* infection and allergy.

Another recent study reported a positive relationship between *H. pylori* colonization and the prevalence of asthma; however, the study did not take a stand on what the underlying mechanism might be, instead pointing to the need for further research [15].

Wang et al. published similar results about the potential association between *H. pylori* infection and the risk of adult-onset asthma [16].

This study reports a positive correlation between *H. pylori* infection and allergic rhinitis and NARES. There are several remarkable studies in the literature. Chen et al. [22] evaluated more than seven thousand participants. The main difference of our study is that our group of patients was composed of subjects with nasal conditions only and excluded other atopic diseases. The number of subjects in our study and control were satisfactory high and the groups were categorized in detail.

The fact that a significant difference was observed only in the adult group and not in the pediatric group deserves special attention. To date, studies examining *H. pylori* have found that interpersonal transmission appears to be the main means of infection [26]. We believe that the pediatric group may not have sufficient time to exhibit nasal conditions caused by the microbe after their initial encounter and so the effects of the microbe on the body are not yet fully described. Thus, there may be a significant difference if the pediatric patients are to be observed over a longer period. This may highlight the issue that eradication of *H. pylori* before the consequences occur.

Still, we are aware that the number of the pediatric participants of this study was quite low and this can cause an involuntary bias so a strong conclusion may not be possible from our results.

H. pylori positivity among the mite allergy, mite and pollen allergy, and NARES groups in the adult study group was significantly higher than in the control group. This suggests a positive correlation between these pathologies and *H. pylori*. In the adult study group, although the positivity rate of patients with pollen allergies was higher than the rate of patients with mite allergies (48.2% and 42.1%, respectively), the difference between patients with pollen allergies and those in the control group was not significantly different (see Table 2). We believe this is because the sample size of the group was not sufficiently large.

We used a *Helicobacter pylori* Stool Antigen Test (HpSA EIA) because it is highly sensitive and specific. The sensitivity, specificity, and general accuracy of the HpSA tests was found to be 68.9%, 100%, and 81%, respectively, with a positive predictive value of 100% [27]. HpSA was reported to be the most accurate test for diagnosing *H. pylori* before its eradication [28].

One method for evaluating these results in a causative manner would be to trigger an allergic response after the immune response against *H. pylori* infection has been detected in the host organism. Existing studies report that the aforementioned bacteria can be isolated from the oropharynx, the nasopharynx, and even the middle ear cavity [29]. Again, the high *H. pylori* positivity rates in NARES

patients may be the result of local eosinophilic responses in *H. pylori*-contaminated areas or of the common mucosal eosinophilic reaction against *H. pylori* throughout the body, which in turn could cause rhinitis symptoms. This may be obvious, however, there remain issues in need of clarification in future research.

Conclusion

Forthcoming studies would undoubtedly question our data, our investigation into the reasons behind these data, and the evaluation of the profits of treating allergic nasal conditions by treating the aforementioned bacterial infection. While our investigations at this level have not reached a scientifically admissible state, our clinical experience has shown a subjective decrease in allergic symptoms in *H. pylori*-positive allergic rhinitis and NARES patients who have been treated for *H. pylori* infection.

Compliance with ethical standards

Conflict of interest The authors have no funding, financial relationships or conflicts of interest to disclose.

References

1. Beasley R (1998) Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 351(9111):1225–1232. [https://doi.org/10.1016/s0140-6736\(97\)07302-9](https://doi.org/10.1016/s0140-6736(97)07302-9)
2. Strachan DP (1989) Hay fever, hygiene, and household size. *BMJ* 299(6710):1259
3. Martinez FD, Stern DA, Wright AL, Taussig LM, Halonen M (1995) Association of non-wheezing lower respiratory tract illnesses in early life with persistently diminished serum IgE levels. *Group Health Med Assoc Thorax* 50(10):1067–1072
4. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM (1997) The inverse association between tuberculin responses and atopic disorder. *Science* 275:77–79
5. Shaheen SO, Aaby P, Hall AJ, Barker DJ, Heyes CB, Shiell AW, Aaby P, Hall AJ, Goudiaby A (1996) Measles and atopy in Guinea-Bissau. *Lancet* 347:1792–1796
6. Bamford KB, Fan X, Crowe SE et al (1998) Lymphocytes in the human gastric mucosa during *Helicobacter pylori* have a T helper cell 1 phenotype. *Gastroenterology* 114:482–492
7. Cremonini F, Gasbarrini A (2003) Atopy, *Helicobacter pylori* and the hygiene hypothesis. *Eur J Gastroenterol Hepatol* 15:635–636
8. McCune A, Lane A, Murray L et al (2003) Reduced risk of atopic disorders in adults with *Helicobacter pylori* infection. *Eur J Gastroenterol Hepatol* 15:637–640
9. Radon K, Windstetter D, Eckart J et al (2004) Farmerexposure in childhood, exposure to markers of infections and the development of atopy in rural subjects. *Clin Exp Allergy* 34:1178–1183
10. Von Mutius E, Illi S, Hirsch T, Leupold W, Keil U, Weiland SK (1999) Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J* 14(1):4–11
11. Uter W, Stock C, Pfahlberg A et al (2003) Association between infections and signs and symptoms of 'atopic' hypersensitivity-results of a cross-sectional survey among first-year university students in Germany and Spain. *Allergy* 58(7):580–584
12. Jarvis D, Luczynska C, Chinn S, Burney P (2004) The association of hepatitis A and *Helicobacter pylori* with sensitization to common allergens, asthma and hay fever in a population of young British adults. *Allergy* 59(10):1063–1067
13. Holster IL, Vila AM, Caudri D et al (2012) The impact of *Helicobacter pylori* on atopic disorders in childhood. *Helicobacter* 17(3):232–237
14. Ma ZF, Majid NA, Yamaoka Y, Lee YY (2016) Food Allergy and *Helicobacter pylori* Infection: a systematic review. *Front Microbiol* 7:368
15. den Hollander WJ, Sonnenschein-van der Voort AM, Holster IL et al (2016) *Helicobacter pylori* in children with asthmatic conditions at school age, and their mothers. *Aliment Pharmacol Ther* 43:933–943
16. Wang YC, Lin TY, Shang ST et al (2017) *Helicobacter pylori* infection increases the risk of adult-onset asthma: a nationwide cohort study. *Eur J Clin Microbiol Infect Dis* 36:1587
17. Mungan Z, Pınarbaşı Şimşek B (2017) Gastroesophageal reflux disease and the relationship with *Helicobacter pylori*. *Turk J Gastroenterol* 28(Suppl 1):61–67
18. Spergel JM (2010) Epidemiology of atopic dermatitis and atopic march in children. *Immunol Allergy Clin N Am* 30(3):269–280
19. Nicolaou N, Siddique N, Custovic A (2005) Allergic disease in urban and rural populations: increasing prevalence with increasing urbanization. *Allergy* 60(11):1357–1360
20. Kelly D, Conway S, Aminov R (2005) Commensal gut bacteria: mechanisms of immune modulation. *Trends Immunol* 26:326–333
21. Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, Bonini S (2000) Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 320(7232):412–417
22. Chen Y, Blaser MJ (2008) *Helicobacter pylori* colonization is inversely associated with childhood asthma. *J Infect Dis* 198:553–560
23. Konturek PC, Rienecker H, Hahn EG, Raithel M (2008) *Helicobacter pylori* as a protective factor against food allergy. *Med Sci Monit* 14:452–458
24. Imamura S, Sugimoto M, Kanemasa K, Sumida Y, Okanoue T, Yoshikawa T, Yamaoka Y (2010) Inverse association between *Helicobacter pylori* infection and allergic rhinitis in young Japanese. *J Gastroenterol Hepatol* 25(7):1244–1249
25. Janson C, Asbjornsdottir H, Birgisdottir A et al (2007) The effect of infectious burden on the prevalence of atopy and respiratory allergies in Iceland, Estonia, and Sweden. *J Allergy Clin Immunol* 120(3):673–679
26. Eusebi LH, Zagari RM, Bazzoli F (2014) Epidemiology of *Helicobacter pylori* infection. *Helicobacter* 19(Suppl 1):1–5
27. Ceken N, Yurtsever SG, Baran N, Alper E, Buyrac Z, Unsal B (2011) Comparison of *Helicobacter pylori* antibody detection in stool with other diagnostic tests for infection. *Asian Pac J Cancer Prev* 12(4):1077–1081
28. Kazemi S, Tavakkoli H, Habizadeh MR, Emami MH (2011) Diagnostic values of *Helicobacter pylori* diagnostic tests: stool antigen test, urea breath test, rapid urease test, serology and histology. *J Res Med Sci* 16(9):1097–1104
29. Saki N, Samarbafzadeh AR, Jonaky RS, Noori SM, Kayedani GA, Nikakhlagh S (2014) The prevalence rate of *Helicobacter pylori* infection in chronic otitis media with effusion patients. *Jundishapur J Microbiol* 7(3):e15694

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.