Helicobacter pylori and Respiratory Diseases

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Helicobacter pylori (H. pylori) is a Gram-negative bacterium involved in the development of gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue. Unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura and vitamin B12 deficiency have also been related to H. pylori infection, whereas for other extra-gastric diseases, the debate is still open. In this entry, we evaluate and discuss the potential involvement of H. pylori infection in the pathogenesis of several respiratory diseases.

Keywords: respiratory diseases ; asthma ; chronic obstructive pulmonary disease

1. Introduction

Helicobacter pylori (H. pylori) infection is globally widespread, usually acquired during childhood, and often related to low socio-economic class [1]. Although the precise mode of transmission remains unproven, it has been shown that such a microorganism spreads directly from one person to another, mainly by fecal-oral or oral-oral routes [2]. This microaerophilic, Gram-negative bacterium is usually located within the mucus layer of the stomach, and certain ultrastructural details found on its surface (sheathed flagella and urease) are involved in its ability to survive in the surrounding hostile environment [3]. Thus, this disproves the ancient conception of the impossibility for microorganisms to survive in the gastric compartment due to acidity [4]. It is well known that H. pylori infection may lead to gastritis, peptic ulcer disease (PUD), gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [5], although most infected subjects remain asymptomatic. Furthermore, in the past few years, the possible role of H. pylori in many extra-gastric diseases has been investigated [6][7][8]. Among these, accumulating evidence also supports an association with neurodegeneration [9] and nonalcoholic fatty liver disease [6], although some controversy still exists. However, only unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency have been associated with the latter infection, as reported in the fifth edition of the Maastricht/Florence Consensus Report (2017) [10].

Respiratory diseases represent a leading cause of morbidity and mortality in the world. For this reason, as stated by the World Health Organization (WHO), the prevention, control and cure of these diseases must be a top priority in global decision-making in the health sector [11]. Currently, infections are the leading cause of respiratory diseases in both children and adults, with variable outcomes depending on the causal agent as well as on the host and environmental factors. Since known etiologic agents and risk factors explain the pathogenesis of only a proportion of cases, investigating whether non-traditional agents have a causal role in the pathogenetic steps of respiratory diseases is of primary importance.

Early epidemiologic studies on the relationship between H. pylori infection and respiratory diseases have been supported by the findings on animal models showing that the presence of the microorganisms in the gastric compartment could be associated with lung injury, as indicated by the increased expression of inflammatory mediators and markers of endothelial dysfunction [12]. Over time, a series of publications, mainly reporting the findings of epidemiologic studies, has focused on this issue and has provided controversial results.

2. Analysis on Results

Considering that several studies did not show a causal relationship, but often, an inverse association between H. pylori infection and allergic asthma [13][14], a protective effect of this microorganism against allergic diseases including asthma, especially in children and young people, was hypothesized around fifteen years ago (the so-called “hygiene hypothesis”). The authors associated the reduction of H. pylori prevalence with the rise in asthma cases as well as other allergic disorders in children, assuming a possible relationship [15]. Over time, multiple epidemiological studies were performed on this topic and a recent meta-analysis, including 18 observational studies with 17,196 enrolled children, reported a significant negative association between H. pylori and the risk for childhood asthma (odds ratio [OR] = 0.68; 95%

confidence interval [CI]: 0.54–0.87; p = 0.002), particularly in those harboring the more virulent strains (according to cytotoxin-associated gene A [CagA] status) (OR = 0.58; 95% CI: 0.35–0.96; p = 0.034). No significant difference among studies regarding participant age, geographical region, study design and diagnostic method for H. pylori detection was observed [16]. In recent years, the association between asthma or other allergic diseases and H. pylori has been intensively investigated. In a case-control study including more than 10,000 patients, H. pylori infection was found in 31%, asthma in 10.4%, and allergic rhinitis in 16% of them, without any significant association; however, in patients with abdominal obesity, H. pylori infection was associated with 30-40% reduced OR of asthma and 25% reduced OR of allergic disorders [17]. Moreover, in a case-control study performed in Greece including 27 pediatric patients with asthma and 54 controls, an inverse association between H. pylori and asthma was confirmed (OR = 0.1; 95% CI: 0.039–0.305; p = 0.026) [18]. In a cohort study, 16% of children who were uninfected at 2 and 10 years of age developed asthma at 16 years vs. none of the children with H. pylori infection at 2 years of age [19] (**Table 1**).

Table 1. Summary of the cumulative results of the main studies included.

Respiratory Disease	Result		Reference	Publication Year
ASTHMA	Meta-analysis of 18 studies	Negative association with *H. pylori* infection	[15]	2021
	Case-control study including 10,000 patients	Only in obese patients *H. pylori* associated with 30–40% OR of asthma ↓	[16]	2019
	Cohort study	16% of children uninfected at 2 and 10 years developed asthma at 16 years versus none of the children with *H. pylori* at 2 years	[18]	2020
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	Case-control study including patients with type 2 diabetes mellitus and controls	In diabetics, seropositivity was significantly associated with chronic bronchitis	[20]	2020
	Retrospective cohort study (Taiwan)	Significant association between *H. pylori* and COPD	[21]	2017
	Case-control study (Korea, country with high burden of *H. pylori*)	No association between *H. pylori* and COPD	[22]	2016

Nevertheless, some authors consider H. pylori only a marker of poor household hygiene. This stems from the evidence from studies testing the hypothesis of a protective effect in relation to asthma in populations with poor hygiene and low H. pylori prevalence (for example in Malaysia and Indonesia), which did not confirm this effect [23]. Furthermore, the results of studies and consequently meta-analyses could be affected by the diagnostic method used to diagnose H. pylori infection (mainly serology that does not discriminate between current and past infection).

In this context, it has been hypothesized that the inhalation of H. pylori or its endotoxins into the respiratory tract could lead to a chronic activation of inflammatory mediators. In 1998, Tsang et al. first described a significantly higher serum IgG positivity against H. pylori in 100 consecutive patients with bronchiectasis compared to healthy controls (76.0% vs. 54.3% respectively, p = 0.001) [24]. The following year, Tsang et al. reported a higher H. pylori CagA+ seroprevalence in bronchiectasis patients than in controls (24% vs. 11.7%, p = 0.03) [25]. However, Angrill et al. were unable to detect H. pylori by histochemical and immunochemical staining in bronchial tissue from patients with bronchiectasis and positive serology [26]. Similarly, Gülhan et al. did not find evidence of H. pylori DNA in either BAL fluid or in lung tissues by using PCR, from patients with bronchiectasis. In addition, they did not find a statistically significant difference in anti- H. pylori IgG level between patients and controls [27]. Furthermore, in another study, there were no significant differences between bronchiectasis patients and controls regarding H. pylori positivity in BAL fluid, gastric juice, and urea breath test [28].

Few studies have examined a possible correlation between H. pylori and cystic fibrosis. Drzymała-Czyż et al. assessed the prevalence of H. pylori infection, using breath tests with isotope-labeled urea in 79 cystic fibrosis patients compared to 302 healthy controls, but no significant difference was found [29]. In a study by Yahav et al., the authors found a lower prevalence of H. pylori infection in cystic fibrosis patients than in non-cystic fibrosis controls (16.6% and 30.0%, respectively), assessed by using specific monoclonal antibodies for fecal H. pylori antigen. However, due to the small number of cystic fibrosis patients enrolled (n = 30) in this study, the difference was not statistically significant [30]. A seroprevalence study, conducted by Israel et al., included 70 cystic fibrosis patients. The authors reported an initial

seropositivity rate of 47% (33/70) for H. pylori IgG antibody, but after pre-adsorption of these sera with Pseudomonas proteins, a marked decrease in H. pylori seropositivity (8%, 6/70) was observed, highlighting a cross-reactivity between H. pylori antigens and Pseudomonas antibodies [31].

3. Conclusions

The question as to whether H. pylori is an innocent bystander, a protective agent or a trigger of respiratory diseases cannot yet be answered. On the other hand, these are often multifaceted disorders, the mechanism of which cannot be explained by only one cause. Hence, the need for larger studies with appropriate epidemiological design to investigate a potential causal relationship between H. pylori infection and respiratory diseases is evident.

References

1. McColl, K.E. Clinical practice. Helicobacter pylori infection. N. Engl. J. Med. 2010, 362, 1597–1604.
2. Delport, W.; van der Merwe, S.W. The transmission of Helicobacter pylori: The effects of analysis method and study population on inference. Best Pract. Res. Clin. Gastroenterol. 2007, 21, 215–236.
3. Fagoonee, S.; Pellicano, R. Helicobacter pylori: Molecular basis for colonization and survival in gastric environment and resistance to antibiotics. A short review. Infect. Dis. 2019, 51, 399–408.
4. Charitos, I.A.; D'Agostino, D.; Topi, S.; Bottalico, L. 40 years of Helicobacter pylori: A revolution in biomedical thought. Gastroenterol. Insights 2021, 12, 111–135.
5. Pellicano, R.; Ribaldone, D.G.; Fagoonee, S.; Astegiano, M.; Saracco, G.M.; Mégraud, F. A 2016 panorama of Helicobacter pylori infection: Key messages for clinicians. Panminerva Med. 2016, 58, 304–317.
6. Buzás, G.M. Helicobacter pylori and non-alcoholic fatty liver disease. Minerva Gastroenterol. Dietol. 2020, 66, 267–279.
7. Pellicano, R.; Ianiro, G.; Fagoonee, S.; Settanni, C.R.; Gasbarrini, A. Review: Extragastric diseases and Helicobacter pylori. Helicobacter 2020, 25 (Suppl. 1), e12741.
8. Doulberis, M.; Papaefthymiou, A.; Polyzos, S.A.; Bargiotas, P.; Liatsos, C.; Srivastava, D.S.; Zavos, C.; Katsinelos, P.; Kountouras, J. Association between active Helicobacter pylori infection and glaucoma: A systematic review and meta-analysis. Microorganisms 2020, 8, 894.
9. Doulberis, M.; Kotronis, G.; Gialamprinou, D.; Polyzos, S.A.; Papaefthymiou, A.; Katsinelos, P.; Kountouras, J. Alzheimer's disease and gastrointestinal microbiota; impact of Helicobacter pylori infection involvement. Int. J. Neurosci. 2021, 131, 289–301.
10. Malfertheiner, P.; Megraud, F.; O'Morain, C.A.; Gisbert, J.P.; Kuipers, E.J.; Axon, A.T.; Bazzoli, F.; Gasbarrini, A.; Atherton, J.; Graham, D.Y.; et al. Management of Helicobacter pylori infection—The Maastricht V/Florence Consensus Report. European Helicobacter and Microbiota Study Group and Consensus panel. Gut 2017, 66, 6–30.
11. Forum of International Respiratory Societies. The Global Impact of Respiratory Disease—Second Edition. Sheffield, European Respiratory Society. 2017. Available online: www.https://www.who.int/gard/publications/The_Global_Impact_of_Respiratory_Disease.pdf (accessed on 30 June 2021).
12. Arismendi Sosa, A.C.; Salinas Ibáñez, A.G.; Pérez Chaca, M.V.; Penissi, A.B.; Gómez, N.N.; Vega, A.E. Study of Helicobacter pylori infection on lung using an animal model. Microb. Pathog. 2018, 123, 410–418.
13. Fullerton, D.; Britton, J.R.; Lewis, S.A.; Pavord, I.D.; McKeever, T.M.; Fogarty, A.W. Helicobacter pylori and lung function, asthma, atopy and allergic disease—A population-based cross-sectional study in adults. Int. J. Epidemiol. 2009, 38, 419–426.
14. Tsang, K.W.; Lam, W.K.; Chan, K.N.; Hu, W.; Wu, A.; Kwok, E.; Zheng, L.; Wong, B.C.; Lam, S.K. Helicobacter pylori sero-prevalence in asthma. Respir. Med. 2000, 94, 756–759.
15. Blaser, M.J.; Chen, Y.; Reibman, J. Does Helicobacter pylori protect against asthma and allergy? Gut 2008, 57, 561–567.
16. Chen, Y.; Zhan, X.; Wang, D. Association between Helicobacter pylori and risk of childhood asthma: A meta-analysis of 18 observational studies. J. Asthma 2021, 8, 1–11.
17. Ness-Jensen, E.; Langhammer, A.; Hveem, K.; Lu, Y. Helicobacter pylori in relation to asthma and allergy modified by abdominal obesity: The HUNT study in Norway. World Allergy Organ. J. 2019, 12, 100035.

18. Tsigalou, C.; Konstantinidis, T.G.; Cassimos, D.; Karvelas, A.; Grapsa, A.; Tsalkidis, A.; Panopoulou, M.; Tsakris, A. Inverse association between Helicobacter pylori infection and childhood asthma in Greece: A case-control study. Germs 2019, 9, 182–187.
19. Melby, K.K.; Carlsen, K.L.; Håland, G.; Samdal, H.H.; Carlsen, K.H. Helicobacter pylori in early childhood and asthma in adolescence. BMC Res. Notes 2020, 13, 79.
20. Siva, R.; Birring, S.S.; Berry, M.; Rowbottom, A.; Pavord, I.D. Peptic ulceration, Helicobacter pylori seropositivity and chronic obstructive pulmonary disease. Respirology 2013, 18, 728–731.
21. Bener, A.; Ağan, A.F.; Al-Hamaq, A.O.A.A.; Barisik, C.C.; Öztürk, M.; Ömer, A. Prevalence of Helicobacter pylori infection among type 2 diabetes mellitus. Adv. Biomed. Res. 2020, 9, 27.
22. Peng, Y.H.; Chen, C.K.; Su, C.H.; Liao, W.C.; Muo, C.H.; Hsia, T.C.; Sung, F.C.; Lai, C.H.; Kao, C.H. Increased risk of chronic obstructive pulmonary disease among patients with Helicobacter pylori infection: A population-based cohort study. Clin. Respir. J. 2017, 11, 558–565.
23. Miftahussurur, M.; Nusi, I.A.; Graham, D.Y.; Yamaoka, Y. Helicobacter, hygiene, atopy, and asthma. Front. Microbiol. 2017, 8, 1034.
24. Tsang, K.W.; Lam, S.K.; Lam, W.K.; Karlberg, J.; Wong, B.C.; Hu, W.H.; Yew, W.W.; Ip, M.S. High seroprevalence of Helicobacter pylori in active bronchiectasis. Am. J. Respir. Crit. Care Med. 1998, 158, 1047–1051.
25. Tsang, K.W.; Lam, W.K.; Kwok, E.; Chan, K.N.; Hu, W.H.; Ooi, G.C.; Zheng, L.; Wong, B.C.; Lam, S.K. Helicobacter pylori and upper gastrointestinal symptoms in bronchiectasis. Eur. Respir. J. 1999, 14, 1345–1350.
26. Angrill, J.; Sánchez, N.; Agustí, C.; Guilemany, J.M.; Miquel, R.; Gomez, J.; Torres, A. Does Helicobacter pylori have a pathogenic role in bronchiectasis? Respir. Med. 2006, 100, 1202–1207.
27. Gülhan, M.; Ozyilmaz, E.; Tarhan, G.; Demirağ, F.; Capan, N.; Ertürk, A.; Canbakan, S.; Ayaşlioğlu, E.; Gülhan, E.; Ahmed, K. Helicobacter pylori in bronchiectasis: A polymerase chain reaction assay in bronchoalveolar lavage fluid and bronchiectatic lung tissue. Arch. Med. Res. 2007, 38, 317–321.
28. Aydın Teke, T.; Akyön, Y.; Yalcin, E.; Ozen, H.; Doğru, D.; Kiper, N.; Ozcelik, U. Does Helicobacter pylori play a role in the pathogenesis of non-cystic fibrosis bronchiectasis? Pediatr. Int. 2016, 58, 894–898.
29. Drzymała-Czyż, S.; Kwiecień, J.; Pogorzelski, A.; Rachel, M.; Banasiewicz, T.; Pławski, A.; Szczawińska-Popłonyk, A.; Herzig, K.H.; Walkowiak, J. Prevalence of Helicobacter pylori infection in patients with cystic fibrosis. J. Cyst. Fibros. 2013, 12, 761–765.
30. Yahav, J.; Samra, Z.; Blau, H.; Dinari, G.; Chodick, G.; Shmuely, H. Helicobacter pylori and Clostridium difficile in cystic fibrosis patients. Dig. Dis. Sci. 2006, 51, 2274–2279.
31. Israel, N.R.; Khanna, B.; Cutler, A.; Perry, M.; Caplan, D.; Weatherly, M.; Gold, B.D. Seroprevalence of Helicobacter pylori infection in cystic fibrosis and its cross-reactivity with anti-pseudomonas antibodies. J. Pediatr. Gastroenterol. Nutr. 2000, 30, 426–431.

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