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REVIEW ARTICLE

Extragastric Manifestations of *Helicobacter pylori* InfectionMarko Banić,^{*†} Francesco Franceschi,[‡] Zarko Babić^{*§} and Antonio Gasbarrini[¶]

*Division of Gastroenterology, University Hospital Dubrava, Zagreb, Croatia, [†]School of Medicine, University of Rijeka, Rijeka, Croatia, [‡]Institute of Internal Medicine, Catholic University of Rome, Rome, Italy, [§]School of Medicine, University of Zagreb, Zagreb, Croatia, [¶]Division of Internal Medicine and Gastroenterology, Catholic University of Rome, Rome, Italy

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Reprint requests to: Francesco Franceschi, Institute of Internal Medicine, Catholic University of Rome, Largo A. Gemelli, 8, 00168 Rome, Italy. E-mail: francesco.franceschi@rm.unicatt.it

Abstract

In the last year, different diseases possibly linked to *Helicobacter pylori* infection but localized outside of the stomach have been investigated. There are, in fact, several studies concerning cardiovascular diseases, hematologic disorders, neurologic diseases, metabolic, hepatobiliary diseases, and other conditions. Some of those studies, such as those on sideropenic anemia and idiopathic thrombocytopenic purpura, are quite large and well conducted, while in other cases there are just small or isolated studies or even case reports. Nonetheless, there is much interest among researchers all over the world for such a topic as demonstrated by the large number of studies published in the last year.

Several articles have been published in the last year concerning the extragastric manifestations of *Helicobacter pylori* infection. Here we summarize the main results obtained by these studies.

Cardiovascular Diseases

Among the extraintestinal manifestations of *H. pylori* infection, ischemic heart disease (IHD) still ranks among the first positions [1,2]. Al-Ghamdi et al. [3] in a recent study reported a higher prevalence of anti-*Chlamydia pneumoniae* and anti-*H. pylori* IgG in patients with acute coronary heart disease (CAD) compared to controls. Interestingly, the presence of anti-*H. pylori* IgG was significantly correlated with high triglyceride level other than IHD in general. Another study performed by Jafarzadeh et al. [4] reported a higher prevalence of *H. pylori*, CMV, and HSV-1 infection in patients with acute myocardial infarction or unstable angina compared to healthy controls. Park et al. [5] performed an interesting study on the association between *H. pylori* infection and coronary artery calcification (CAC) score, starting from the assumption that this score, measured by computed tomography, has previously been used as a screening test for coronary atherosclerosis. Interestingly, among 2,029 subjects enrolled, 59.8% were positive for *H. pylori* infection and multivariate analysis revealed a positive association between *H. pylori* seropositivity and severity of CAC score.

Despite these promising findings, some authors did not find, however, any significant association between *H. pylori* infection and IHD. Padmavati et al., [6] in fact, did not show any association between the occurrence of cardiovascular diseases in general and *H. pylori* in Indian population. Moreover, Schottker et al. [7] in a very large study conducted on German population did not find any significant association between mortality from cardiovascular diseases and *H. pylori* and/or CagA-positivity, and similar results were obtained in a study by Stefler et al. [8] on South Asia population.

In the last year, only one study has been conducted concerning a possible role of *H. pylori* infection on ischemic stroke, showing negative findings [9]. In contrast, one study of our group on a possible role of virulent strains of *H. pylori* on patients with idiopathic dysrhythmia showed positive findings [10]. In particular, we found a higher prevalence of both CagA and VacA-positive *H. pylori* strains in patients with idiopathic dysrhythmia compared to controls [10].

Immunologic Diseases

Previous studies have proposed a possible association between *H. pylori* infection and immunologic diseases [2]. A case report by Campuzano-Maya [11] showed the occurrence of a remission of alopecia areata following *H. pylori* eradication in a 43-year-old man with an

8-month history of such a disease. On the other hand, Holster et al. [12] did not report any significant association between *H. pylori* infection and allergic rhinitis, and atopic dermatitis and physician-diagnosed asthma. However, a higher prevalence of *H. pylori* infection has been shown in children with reported wheezing compared to non-wheezers ($p = .05$) [12]. Another interesting area is that related to the occurrence of asthma and allergy in relation to infections [13]. On this subject, Amberbir et al. [14] in a study from Ethiopia clearly showed that children infected by *H. pylori* have a significant reduced risk of eczema. On the contrary, there was no effect of geohelminths and intestinal microflora on this allergic condition. Arnold et al. [15] performed a study on an animal model of allergic airway disease and *H. pylori* infection; interestingly, *H. pylori* protected animals from airway hyper-responsiveness and prevented allergen-induced pulmonary and bronchoalveolar infiltration by eosinophils, Th2 cells, and Th17 cells. Serrano et al. [16] also confirmed the presence of an inverse relationship between allergy markers and *H. pylori* infection in children, which in turn correlated with elevated levels of TGF- β both locally and systemically. An article published in the New England Journal of Medicine [17] showed that children who lived on farms and who were exposed to an increased range of microbes had a reduced incidence of asthma. In response to these results, Chen & Blaser [18] specified that we should also look for endogenous microbes, such as *H. pylori* other than exogenous, as many authors reported an inverse relation between *H. pylori* infection and asthma in children.

Hematologic Diseases

It is known that *H. pylori* infection is implicated in many nutritional matters, including iron absorption and metabolism [19]. Boyanova [20], in fact, have recently proposed how virulent strains of *H. pylori*, such as those harboring CagA and VacA, work concurrently to provide both iron acquisition from interstitial holo-transferrin and enhanced bacterial colonization of host cells apically. Xia et al. [21] have conducted a survey on anemia and *H. pylori* infection in adolescent girls from the Chinese region Suhia, reporting a significant association between *H. pylori* and iron-deficient anemia (IDA), while Malik et al. [22] clearly showed that the administration of iron in patients with IDA and concomitant *H. pylori* infection is less effective in comparison with the results obtained when patients are successfully cured of *H. pylori* infection. Finally, the association between *H. pylori* infection and IDA is so strong that even the British Society of Gastroenterology

guidelines for the management of IDA indicate *H. pylori* infection to be sought in IDA patients if endoscopy is negative and to be eradicated if present [23]. On the other hand, the role of *H. pylori* in iron deficiency seems to be different in adult and children. In fact, there are several studies showing the absence of a positive association between iron stores and *H. pylori* infection among children [24–28].

Finally, the role of *H. pylori* infection as a possible cause of idiopathic thrombocytopenic purpura (ITP) still remains significant. In fact, Saito et al. [29] demonstrated that the absolute number of plasmacytoid dendritic cells (pDCs), which is generally reduced in patients with ITP, is also reduced in patients with ITP and concomitant *H. pylori* infection. Interestingly, the number of pDCs resulted to be significantly increased after the eradication of *H. pylori* infection in ITP patients [29]. In another study, Sato et al., [30] reported that the development of corpus atrophic gastritis may be associated with *H. pylori*-related ITP, while Kikuchi et al. [31] in a 8-year follow-up of patients with ITP and previous *H. pylori* infection clearly showed that the prognosis of patients who positively increased their platelet count after the eradication of *H. pylori* is usually excellent. Similar results have been reported by Russo et al. [32] on children. Nonetheless, Ohe and Hashino [33] postulated that the administration of macrolides in patients with ITP may increase the platelet count independently from *H. pylori* infection, through an immunomodulatory effect intrinsic to the drug.

Neurologic Diseases

Deretzi et al. [34] have been explaining the link of neurodegenerative disorders and neuroinflammation that could be potentially initiated by peripheral conditions through disrupted blood–brain barrier. According to these authors, the pathogens, including *H. pylori*, may access the central nervous system (CNS) through blood, the nasal olfactory pathways, and the gastrointestinal system, especially in regard to the fact that gastrointestinal immune system (GIS) represents a primary immune organ with specialized immunoregulatory and anti-inflammatory functions. *H. pylori* would be capable of inducing humoral and cellular immune responses that, owing to the sharing of homologous epitopes (molecular mimicry), cross-react with CNS components thereby contributing and possibly perpetuating neural tissue damage. Thus, *H. pylori* would be implicated in the development and regulation of several autoimmune and degenerative diseases of the CNS. Shiota et al. [35] found no association between *H. pylori* infection and Alzheimer's disease in a Japanese cohort of patients. In

their commentary, Kountouras et al. [36] stressed out that this study was underpowered, owing to small number of patients enrolled and relatively high *H. pylori* infection prevalence in general Japanese population; thus, the study would not be comparable to European studies indicating the association between *H. pylori* infection and Alzheimer's disease. Based on the studies published previously, several authors hypothesized that *H. pylori* infection could indirectly affect neural and brain tissue by disrupting the brain–neural barrier and blood–brain barrier, by release of numerous proinflammatory cytokines (IL-1 β , IL-6, TNF- α), acting at the distance and being involved in pathogenesis of inflammatory demyelinating neuropathies [37], and epilepsy [38]. The underlying mechanism of a probable association between *H. pylori* infection and epilepsy would be the action of TNF- α , leading to upregulation of matrix metalloproteinases that cause the disruption of the blood brain barrier.

Diabetes mellitus and Metabolic Disorders

A high prevalence of *H. pylori* infection was reported by several authors in patients with diabetes mellitus (DM), but the clinical consequences in terms of metabolic control seem to be low [2]. In a review article [39], Albaker stressed out that the association between DM and *H. pylori* infection remains controversial, although some studies showed a high prevalence of this infection in both Type 1 DM and Type 2 DM. Although some studies spoke in favor of an association of CagA+ virulent strains with microangiopathy, neuropathy, and microalbuminuria in Type 2 diabetic patients, the results of The Freemantle Diabetes Study did not confirm the CagA seropositivity as a risk factor for chronic vascular complications of Type 2 DM [40].

Metabolic syndrome is one of the most prevalent global health problems that predisposes to Type 2 DM and it is linked to insulin resistance. A very interesting study on 462 elderly Koreans supported the hypothesis that *H. pylori* infection plays a role in promoting atherosclerosis by modifying lipid metabolism [41]. In a systematic review, Polyzos et al. [42] represented the results of nine studies reporting data on 2120 participants, in regard to possible association between *H. pylori* infection and insulin resistance measured by a quantitative homeostatic model. A potential association was found, and the interesting points to highlight being that impaired ghrelin production and low levels of leptin in patients with *H. pylori* infection induce elevated fasting insulin levels in insulin-resistant patients and impaired insulin sensitivity, respectively.

Hepatobiliary Diseases

In an interesting Brazilian study of Silva et al. [43], the authors evaluated the association between the presence of *H. pylori* in the liver biopsy specimens determined by PCR and the etiology and stage of hepatic disease and the cytokine pattern (ELISA) displayed by the patients. This prospective study was carried out on 147 patients (106 pts with primary hepatic diseases and 41 with metastatic tumors) and 20 liver donors as controls. According to the results of this study, the detection of *H. pylori* DNA in the liver was independently associated with hepatitis B virus/hepatitis C virus, liver metastases of pancreatic carcinoma. The cytokine pattern was characterized by high IL-10, low or absent IFN- γ , and decreased IL-17A levels ($p < .001$). In addition, the bacterial DNA was never detected in the liver of patients with alcoholic cirrhosis and autoimmune hepatitis that are associated with Th1/Th17 polarization. It is important to stress that gastric *H. pylori* status, as evaluated by ELISA and/or UBT, was positive in 78.9% of patients and in 55% of control liver donors. Taking into account that *H. pylori*-positive serology/UBT status was independently associated with the presence of *H. pylori* DNA in the liver and strains isolated from the liver had similar characteristics to those isolated from the stomach, the authors hypothesize that gastric *H. pylori* can reach the liver by retrograde transfer from the duodenum when cytokine pattern of the host is more regulatory type than proinflammatory type. However, according to the results of this study the regulatory cytokine profile, characterized by IL-10, was detected in a certain number of patients with gastric *H. pylori* infection, but without evidence of *H. pylori* in the liver. However, the host immune response may represent the ability of the liver in clearing certain microorganism, thus reflecting the possibility that the presence of *H. pylori* could be more a consequence rather than a cause of hepatic diseases.

Le Roux-Goglin et al. [44] hypothesized that, under pathologic conditions in vivo, hepatocytes can also assemble podosomes, peculiar dot-like structures made of actin and containing adhesion structures, such as vinculin, integrins, signaling proteins, and membrane-type 1 matrix metalloproteinase. This study for the first time showed that mouse hepatocytes infection with four strains of *H. pylori* that were tested doubled the number of podosome forming cells in vitro, suggesting a common pathogenic mechanism to different strains. Further studies are needed to elucidate the link between induced podosome formation by *H. pylori* infection of hepatocytes in vitro and collagen accumulation as a hallmark of liver diseases, including fibrosis and cancer.

A study of Agrawal et al. [45] was carried out on 65 patients with liver cirrhosis in India to find the prevalence of minimal hepatic encephalopathy (MHE), to establish the correlation between the presence of *H. pylori* infection and hyperammonemia in these patients, and to study the effects of eradication therapy in patients with MHE. The prevalence of MHE was 54% (35/65 pts), while *H. pylori* infection was found in 63% (22/35 pts) with MHE and in 37% (11/30 pts) without MHE. All the patients with MHE were treated with a triple eradication therapy (irrespective of *H. pylori* status) for one week along with lactulose. Among patients with MHE, fasting blood ammonia levels were significantly higher in patients who tested positive for *H. pylori* infection ($1.80 \pm 0.34 \mu\text{g/mL}$) than in those who tested negative (1.39 ± 0.14) ($p < .001$). Interestingly, fasting blood ammonia levels and psychometric tests showed significant improvement after one week of triple eradication therapy (lansoprazole/clarithromycin/tinidazole) along with lactulose, irrespective of *H. pylori* status before treatment.

Ophthalmology, Skin, and Oral Mucosa Diseases

The very active Greek group from University of Thessaloniki led by J. Konturas published several original contributions as well as the reviews concerning the connection between *H. pylori* infection and primary open-angle glaucoma [46,47]. The authors suggested a variety of underlying mechanisms, including the induction of inflammatory responses, as well as apoptotic processes that could lead to glaucomatous neuropathy. The study of Zavos et al. [48] detected *H. pylori* organisms using cresyl fast violet stain on histology preparations of tissue samples of trabeculum and iris, taken from the patients who underwent surgical trabeculectomy for open-angle glaucoma, and who tested positive for gastric *H. pylori* infection. In addition, Zavos et al. [49] evaluated gastric biopsy specimens from 43 patients with open-angle glaucoma for the presence of *H. pylori* and expression of genes, involved in cell proliferation and apoptosis (Ki-67, p53, Bcl-2) as well as indices of cellular immune surveillance (T- and B-lymphocytes). Interestingly, the majority of patients with open-angle glaucoma tested positive for gastric *H. pylori* infection (90.7%), and overexpressed Ki-67, p53, and Bcl-2.

In regard to dermatologic diseases, an improvement of chronic urticaria after eradication of *H. pylori* infection was reported for several cases [50].

Two recent articles by Radic et al. [51] and Zan & Nakanuma [52] reviewed the literature, including the role of *H. pylori* in chronic inflammatory conditions,

such as systemic sclerosis (SSc) and autoimmune pancreatitis. In the pathogenesis of SSc, possibly linked to *H. pylori* infection, the authors proposed molecular mimicry, endothelial cell damage, superantigens, and microchimerism, emphasizing that development of SSc is unlikely to depend exclusively on an infectious agent, but would be the result of interactions between infectious agent(s) and a cascade of host-specific factors and events. Immunoglobulin G-4 disease represents a unique inflammatory condition that induces tumorous swelling of affected organs, histologically characterized with diffuse lymphoplasmacytic infiltration of affected organ, occasional eosinophils, storiform fibrosis, obliterative phlebitis, infiltration by numerous IgG4-bearing plasma cells, and marked clinically by dramatic response to steroid therapy [53]. Autoimmune pancreatitis (AIP) seems to be the prototype of an IgG4-related disease, suggesting that gastric *H. pylori* infection triggers AIP in genetically predisposed individuals through molecular mimicry with plasminogen-binding protein of *H. pylori* exhibiting homology to ubiquitin-protein ligase E3 component n-recogin 2, an enzyme expressed in pancreatic acinar cells [54]. However, serum IgG4 levels were elevated in only 53% of patients in the mentioned study, suggesting that the cohort assessed might, in substantial part, represent non-IgG4-related AIP (type II AIP).

An interesting study by Bago et al. [55] involved 56 patients with UBT-proven *H. pylori* infection, and 41.1% of patients harbored the bacterium in oral cavity, as detected by PCR. Three months after the triple eradication therapy (PPI twice daily/amoxicillin/clarithromycin), the eradication rate in stomach was 78.3%, and surprisingly, *H. pylori* was not detected in any sample from oral cavity. The results of this study are not in agreement with the hypothesis that the oral cavity may represent the reservoir for gastric reinfection.

Nasal, Oropharyngeal, and Laryngeal Disorders

A Polish study by Burduk et al. [56] investigated on the possible *H. pylori* colonization in chronic rhinosinusitis and benign laryngeal diseases. This prospective, controlled study involved a series of 30 patients with nasal polyps and normal nasal mucosa and 30 patients with benign laryngeal diseases who underwent endoscopic sinus and endolaryngeal surgery. DNA was extracted from fresh tissue samples and subjected to PCR analysis for detection of *ureA* and *cagA* *H. pylori* gene. Tissue samples were positive for *ureA* in all the patients involved in the study, and *cagA*⁺ was identified in 23.3% of patients with laryngeal disease while no

positive result for *cagA*⁺ was observed in patients with nasal polyps and concha bullosa.

Extragastric Malignancies

In a review, Bulajic et al. [57] examined the studies conducted in the last 10 years, in regard to possible correlation between *Helicobacter* spp. and extragastric malignancies of digestive system. The PCR subtype most widely used in evaluated studies was nested PCR, and genes targeted most frequently for amplification were 16S rDNA of *Helicobacter* spp and *ureA* or *cagA* genes of *H. pylori*. A strong correlation between *Helicobacter* spp. colonization and primary liver tumors as well as bile duct tumors was found, whereas the results were contradictory for pancreatic cancer, demanding further investigation. There was no proven correlation between *Helicobacter* spp. and colorectal cancer. However, in another review, Risch summarized and analyzed seven published studies (three case-control studies and four cohort studies) with regard to pancreatic cancer odds ratio (OR) for *H. pylori* positivity [58]. The author found that *H. pylori* colonization significantly increased the risk for pancreatic cancer, with a pooled OR for this combined analysis of 1.65 (95% CI: 1.30–2.09). In light of a published case-control study that showed increased risk of pancreatic cancer with non-O blood groups (A, B, and AB) compared to O [59]. Risch postulated that *N*-nitroso compounds have blood-borne trophic effects on pancreatic ductular epithelium that act combined with *H. pylori* infection, embedded in the background of host genetic variations and ABO that may affect other aspects of inflammatory response, could lead to development of pancreatic cancer.

Koshiol et al. [60] conducted the study of 350 lung adenocarcinoma cases, 350 squamous cell carcinoma cases, and 700 nested controls within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) cohort of male Finnish smokers. To test the associations between *H. pylori* seropositivity (ELISA) and lung cancer risk using conditional logistic regression, controls were one-to-one matched by age and date of baseline serum draw. The results of this study did not found an association between *H. pylori* seropositivity and either adenocarcinoma (OR 1.1, 95% CI: 0.75–1.6) or squamous cell carcinoma (OR 1.1, 95% CI: 0.77–1.7), and the results were similar for *CagA*⁻ and *CagA*⁺ *H. pylori* seropositivity. Nevertheless, these results should be considered in regard to the relatively high *H. pylori* seropositivity in 79.7% of cases and in 78.5% of controls. Still, a possible association between *H. pylori* infection and lung cancer remains intriguing because lungs develop embryologically from the same

endodermal cells that line the GI tract and contain cells that produce peptide hormones like gastrin, leaving open the possibility that trophic effects in conjunction with systemic effects of local inflammation (*H. pylori* lipopolysaccharide) may promote cellular proliferation in the lungs, as well.

Conclusions

In conclusion, in the last year, several diseases have been investigated for a possible association with *H. pylori* infection. Considering the high number of papers published so far, we may easily state that this topic is still one of the most fascinating inside the *H. pylori* research area.

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