EXTRAGASTRIC MANIFESTATIONS OF HELICOBACTER PYLORI INFECTION

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Abstract: *Implications of Helicobacter pylori infection in esogastroduodenal pathology are well known. A lot of studies focused on the pathological properties of this bacteria have suggested its involvement in the ethiological determinism of some extragastric diseases, far beyond gastric colonization. For some of them, the role of Helicobacter pylori has been already proved (idiopathic thrombocytopenic purpura, iron deficiency anemia), but its etiopathogenic impact is still unclear with reference to other morbid entities (ischemic heart disease, diabetes mellitus, Alzheimer`s disease).*

Cuvinte cheie: *Helicobacter pylori, infecție, manifestări extragastrice*

Rezumat: *Implicațiile infecției cu Helicobacter pylori (Hp) în patologia esogastroduodenală sunt binecunoscute. Numeroasele studii care s-au concentrat asupra valențelor patologice ale bacteriei au sugerat intervenția acesteia în etiopatogenia unor boli extragastrice, depăşind cu mult zona anatomică antrală de colonizare gastrică. Pentru unele patologii, determinismul infecției cu Hp este cert dovedit (purpura trombocitopenică autoimună, anemia feriprivă), impactul etiopatogenic fiind încă neclar cu referire la alte entități morbide (boala cardiacă ischemică, diabetul zaharat, boala Alzheimer)*

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Since the first report ofWarren and Marshall in 1983 regarding the Helicobacter pylori, the authors suspected this bacteria to be implicated in some gastroduodenal diseases. Thousands of studies dissected with fervour this interrelation, unequivocally demonstrating the central role of Hp in the genesis of gastric and duodenal ulcer (1,2,3), gastritis (4) and stomach cancer (5,6). Meanwhile, a series of observations have expanded the Hp pathophysiological impact to the esogastroduodenal region until absolutly unexpected areas, such as cardiovascular and neurological pathology or diabetes mellitus. Extragastric manifestations of Helicobacter pylori infection continues to capture the attention of researchers worldwide, many studies habe been published in recent years.

***Cardiovascular pathology*.** The role of inflammation in the pathogenesis of coronary artery disease, via atherosclerosis, was clearly stated (7,8). It has been demonstrated that the infection with Helicobacter pylori is associated with an inflammatory response that includes increases of TNF- α, interleukin Ib, reactive C protein, intercellular adhesion molecules (ICAM-1) and vacular adhesion mollecules (VCAM-1)(9,10,11). Given the long persistence of bacteria in gastric mucosa, often for life, we can accept the idea that the subsequent inflammatory response has a chronic nature, though of low intensity, as demonstrated by Graham in 1989 (12). Systemic inflammatory response and ischemic heart disease would be associated mainly with strains expressing cagA virulence factor (13). Other recent studies reached to a similar conclusion (14, 15). Another mechanism for promoting inschemic heart disease would be the interaction between Hp and von Willebrand factor which would determine, by binding to glycoprotein Ib, platelet aggregation and thrombosis (16).

Diabetes mellitus. Recently (2009) was published the first study to demmonstrate the presence of insulin secretory disfunction in patients infected with cagA+ strains (17). Other previous studies, based on epidemiological data, showed association of Helicobacter pylori infection with increased incidence of diabetes mellitus (18). On the other hand, Ojetti et al. showed a growth rate of reinfection in diabetic patients, suggesting a reciprocal determinism (19).

Hematological pathology

Idiopathic thrombocytopenic purpura (ITP). Helicobacter pylori is a known cause of idiopathic thrombocytopenic purpura (20,21). Pathogenetic mechanism appears to be the existence of a structural similarity between a platelet component, that is a receptor for von Willebrand factor, and vacuolated cytotoxin secreated by cagA+ strains, which would trigger an immune cross response (22). Eradication of bacteria in patients with ITP would significantly increase the response to treatment (23).

Iron deficiency anemia. Helicobacter pylori association with iron deficiency anemia has as the main substrate obvious or occult bleeding due to the induced gastroduodenal pathologies (ulcers, ulcerations, cancer). Low ferritin and ascorbic acid levels in patients infected with cagA+ strains (24) and decrease iron absorption in patients with chronic atrophic gastritis are incriminated too.

Dermatological pathology. Recent studies suggest that Hp may play a role in the pathogenesis of various skin diseases, particulary chronic urticaria. The intervention of bacteria would be not as a trigger, but as a factor which facilitate the exacerbations of this pathology (25). As for other dermatological diseases, such as alopecia areata and Behcet`s

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disease, involving Helicobacter pylori was not demonstrated (26, 27).

Ophthalmological pathology. Idiopathic central serous corioretinopathy is more common in patients infected with Hp (28) and tend to have a higher incidence of remission after eradication of bacteria (29). It has been demonstrated (30) that patients with normal tension glaucoma have a higher prevalence of infection with Helicobacter pylori, indicating a possible role of bacteria in the promotion or evolution of this eye disease

Neurological pathology. A recent study (31) has shown increased levels of anti-Hp IgG in cerebrospinal fluid of patients with Alzeimer`s disease. Eradication of bacteria has led to significant improvements in clinical manifestations (32). Helicobacter pylori appear to play a role in idiopathic Parkinsonism (33).

Obesity. It has been demonstrated (34) that the Helicobacter pylori eradication predisposes to obesity. Oxyntic gastric glands contain cells that regulate appetite through ghrelin pathway. This hormone has orexigen effect, stimulates gastric secretion and motility and inhibits secretion of leptin with anorexogenic role. Aggressive strains of Hp promote a potent gastric inflammatory response, followed by gastric atrophy, which decrease gastric and systemic ghrelin levels (35). The disappearance of the bacteria in the gastric mucosae upregulates GR ghrelin secreting cells, which makes it possible to promote appetite and weight gain.

Gynecologic pathology. There is evidence suggesting the involvement of Helicobacter pylori in various obstetrical and gynecological morbid circumstances, such as pre-eclampsya (36), hyperemesis gravidorum (37) or polycystic ovary syndrome (38).

Hepatobiliary pathology. Infection with Helicobacter pylori is accepted as a precipitating factor in gallstone formation and recent studies (39,40) showed the presence of bacteria in the hepatobiliary system. Ki et al conducted a study (41) that demonstrates that Helicobacter pylori association with increassed levels of TGF-β1 may accelerate liver fibrosis by proinflammatory signaling pathways from hepatic stellate cells.

Pulmonary pathology. Researchers have noticed recently a positive correlation between the seroprevalence of Hp and lung neoplasm and propose as pathophysiological mechanism the increased levels of gastric, whose role in promoting cell proliferation and angiogenesis is well known; these effects would exercise on bronchial epithelium too (42,43). It was also published a study (44) focused on a case of sarcoidosis cured after Helicobacter pylori eradication..

CONCLUSIONS

In conclusion, we can say that, currently, the involvement of Hp has been clearly proven for some extragastric pathologies (idiopathic thrombocytopenic purpura, iron deficiency anemia), but questions remain concerning the role of bacteria in other diseases, which leaves open area of research aimed to clarify the unknown valences of Helicobacter pylori.

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