Scripta Scientifica Medica, 2010; vol. 42 (1), pp 51-53

THE ROLE OF HELICOBACTER PYLORI INFECTION IN AUTOIMMUNE AND ALLERGIC DISEASES

Bankova A., M. Benkova, I. Dobreva, P. Tasheva and B. Varbanova

Department of Paediatrics and Medical Genetics,
Medical University of Varna "Prof. Dr. "Paraskev Stoyanov"

Reviewed by: Prof. A. Klisarova

ABSTRACT

The role of *H. pylori* in the pathogenesis of variety gastric diseases such as chronic active gastritis, peptic ulcer disease, MALT lymphoma, and gastric adenocarcinoma is well established. In this paper we review the pathogenic mechanisms involved in some autoimmune and allergic diseases shown to be related to *H pylori* infection.

Key words: Helicobacter pylori, Autoimmunity, Allergy

The role of Helicobacter pylori (*H. pylori*) in the pathogenesis of chronic active gastritis, peptic ulcer disease, MALT lymphoma, and gastric adenocarcinoma is well established. In the recent years an increasing number of extragastroduodenal conditions have been related to H pylori infection. In the following article we discuss the role of H. pylori in the pathogenesis of large group of autoimmune and allergic diseases.

The discover of *H. pylori* in 1983 by Warren and Marshall set a new era in our concept of the pathogenesis, diagnosis and treatment of peptic ulcer disease, chronic gastritis and gastric adenocarcinoma.

H. pylori, at first named Campylobacter pyloridis, is a spiral-shaped, Gram negative, microaerophillic, flagellated bacterium. The pathogenetic mechanisms involved in the chronic inflammatory process, which if untreated lead to peptic ulcer disease and gastric adenocarcimoma, have been an issue of extensive studies (16).

In the recent years *H. pylori* is blamed for influencing a large group of extragastroduodenal diseases (18). In contrast to the well established role of *H. pylori* in the gastric pathology, its relation to autoimmunity and allergy still remains unclear. Two completely opposite effects have been observed:

1. High risk of developing various autoimmune diseases in H. pylori infected individuals, such as: autoimmune thyroid diseases, diabetes mellitus and its complication, rheumatoid arthritis, autoimmune atrophic gastritis, pernicious anemia, autoimmune hepatitis, Sjögren disease, Schönlein- Henoch purpura (10), autoimmune pancreatitis, Raynaud's phenomenon
2. Association between the absence of H pylori and the increased risk of various allergic diseases, such as asthma, food allergy, chronic urticaria, atopic dermatitis, and hereditary angioneurotic edema

Address for correspondence:
B. Varbanova, Dept. of Paediatrics,
Medical University Prof. Dr. P. Stoyanov,
55 Marin Drinov Str., 9002 Varna, Bulgaria
e-mail: dr_boriana_varbanova@abv.bg

H. pylori and autoimmune diseases

Autoimmunity is a result of a loss of immunological tolerance. Two mechanisms leading to developing of autoimmunity in *H. Pylori* positive individuals are suggested:

1. molecular mimicry between *H. pylori* antigens and self-peptides and
2. excess production of proinflammatory cytokines, due to persistent inflammatory process results in impaired cellular and humoral immunity (11).

Molecular mimicry has been defined as sequence similarities between foreign and self-peptides. It results in cross-activation of autoreactive T or B cells by pathogen-derived peptides and an immune system failure to recognize self antigens leading to their destruction.

In the group of autoimmune thyroid disorders (autoimmune atrophic thyroiditis and Hashimoto's thyroiditis) high prevelance of *H. pylori* among patients with high titers of thyroid auto-antibodies (anti-Tg and anti-TPO) have been reported. Monoclonal antibodies against Cag-A^+ *H pylori* strains are suggested to cross-react with follicular cells of the thyroid gland (3,6,7,17).

In autoimmine atrophic gastritis and pernicious anemia a combination of the two major mehanisms (molecular mimicry and excess production of proinflammatory cytokines) is discussed. Autoimmune gastritis is associated with autoantibodies directed against 3 antigens: intrinsic factor, parietal cell canaliculi (including H^+/K^+-ATPase) and plasma membrane antigens. In autoimmune atrophic gastri-

tis autoantibodies against H^+/K^+-ATPase are associated with *H. pylori* infection. This state is controversial to the former belief that autoimmune gastritis or type A gastritis is not connected with *H. pylori* infection. H^+/K^+-ATPase autoantigen has been proven to be the target for autoreactive T cells, that are responsible for the destruction of the gastric mucosa (2).

In pernicious anemia molecular mimicry between *H. pylori* antigens and the H^+/K^+-ATPase, which lead to irreversible destruction of the gastric body mucosa, is suggested (12).

Microalbuminuria in diabetes mellitus as initial sign of nephropathy in *H. pylori* positive patients is combination of the two pathogenetic mechanisms:

1. Cag-A-positive strains are associated with the increased production of cytokines such as tumor necrosis factor, interleukin -1, -6, and -8 that might alter the control of glycemia in diabetic patients
2. antigenic sequences similarities between *H. pylori* antigens and endothelial cells of the tubules cause immunomediated injury at the level of the endothelium, leading to albumin leakage (14).

H. pylori infection can trigger autoimmune pancreatitis in genetically predisposed subjects. Significant homology between human carbonic anhydrase II and alpha-carbonic anhydrase of *H. pylori* (an enzyme which is fundamental for the survival and proliferation of the bacterium in the gastric environment) is suggested (9).

H. pylori and allergic diseases

In contrast to the trigger role of *H. pylori* in autoimmune diseases, its presence probably protect from allergic and autoinflammatory diseases.

Except for the two main pathogenetic mechanisms involved in the autoimmunity in *H. pylori* posistive individuals, third theory is discussed - the hygiene hypothesis.

The hygiene hypothesis, proposed by David P. Strachan, is based on the interaction between Th1 and Th2 cells. Many infectious agents elicit a TH1-mediated immune response (cellular immunity), which down-regulates TH2 responses (humoral immunity) (5).

The absence of certain levels of pathogens suppresses the TH1 arm of the immune system and stimulates the TH2 arm, which in turn lead to allergic diseases.

Bronchial asthma and allergic diseases are connected with production of Th2 cytokines, such as interleukin-4 (IL-4) and IL-5, and are inhibited by Th1 responses.

As *H. pylori* prevalence has declined, the presence of allergic disorders, especially those that appear during childhood, has risen. The reduced incidence of colonization with cagA+ strains (increased incidence of acagia) increases the incidences of allergic disorders (4).

Among several bacterial factors, the neutrophil-activating protein of *H. pylori* (HP-NAP) plays a key role in driving Th1- and inhibiting Th2 - responses *in vitro* and *in vivo* in allergic bronchial asthma in humans. Both systemic and mucosal administrations of HP-NAP are successful in reducing eosinophilia, Ig E and systemic Th2 cytokines at the bronchial level (1).

This argument is used to explain epidemiological data indicating a low prevalence of allergic disorders in developing countries presenting a high incidence of bacterial infections, including *H. pylori* infection. In contrast, an increasing prevalence of allergic disorders occurs in Western countries where the incidence of bacterial infections is low.

The association between *H. pylori* infection and food allergy (8), as well as with other allergic diseases like chronic urticaria, atopic dermatitis, and hereditary angioneurotic edema is suggested, although contradictory results have been obtained.

Urticaria has been reported to be associated with a number of infections: hepatitis B virus, *Streptococcus* and *Mycoplasma* species, *Helicobacter pylori*, *Mycobacterium tuberculosis*, and herpes simplex virus.

A possible relationship between chronic idiopathic urticaria (CIU) and *H. pylori* infection has been suggested in studies, in which antibiotic eradication of the pathogen leads to regression of urticaria in up 100% of cases. The pathogenesis of this relationship still remains unclear and requires further assessment.

The prevalence of *H. pylori* infection has been reported to be lower in individuals with inflammatory bowel disease (IBD). The mechanisms responsible for this are unknown. The lower prevalence of *H. pylori* infections in patients with IBD might be due to better hygiene and sanitation during childhood and adolescence, and this may have predisposed them to IBD. Improvements in living standards, including better nutrition, safer food, clean water, and improved hygienic facilities, have led to a progressive decline in the incidence of infectious diseases and have increased immune disorders, due to inappropriate immunopathologic responses to autoantigens, allergens, and/or antigens (13,15).

CONCLUSION

The discovery of *H. pylori* provoked large spectrum of investigations, which revealed its role in the pathogenesis of chronic gastritis, peptic ulcer disease, gastric adenocarcinoma and MALT-lymphoma.

In 1997 the complete sequence of *H. pylori* was determined and molecular mimicry between *H. pylori* and its human host was established.

Nevertheless, the role of *H. pylori* in the pathogenesis of extragastroduodenal disorders is still not well understood. Despite there are ample evidences of its influence over autoimmune and allergic disorders, further investigations are needed to fully unmask this pathogen.

REFERENCES

1. Amedei A., A. Cappon, G. Codolo et al. The neutrophil-activating protein of Helicobacter pylori promotes Th1 immune responses. *J Clin Invest*., **116**(4), 2006, 1092-101.

2. Bergman M., G. Faller, M. D'Elios et all. Gastric autoimmunity. *Helicobacter pylori-physiology and genetics*, 2001, chapter 36.
3. Bertalot G, G. Montresor , M. Tampieri et al. Decrease in thyroid autoantibodies after eradication of Helicobacter pylori infection. *Clin Endocrinol* (Oxf), **61**, 2004 650-2
4. Cover T., J. Martin. Helicobacter pylori Health and Disease. *Gastroenterology*,**136**, 2009, 1863-1873
5. Cremonini F, A. Gasbarrini. Atopy, Helicobacter pylori and the hygiene hypothesis. *Eur J Gastroenterol Hepatol*, **15**(6), 2003, 635-6
6. De Luis D., C. Varela. Helicobacter pylori infection is markedly increased in patients with autoimmune atrophic thyroiditis. *J Clin Gastroenterol*, **26**, 1998, 259-63.
7. Figura N., G. Di Cairano, F. Lorè et al. The infection by Helicobacter pylori strains expressing CagA is highly prevalent in women with autoimmune thyroid disorders. *J Physiol Pharmacol*, **50**, 1999 817-26
8. Figura N., A. Perrone, C. Gennari et al. Food allergy and Helicobacter pylori infection. *Ital J Gastroenterol Hepatol.* **31**(3), 1999, 186-91.
9. Guarneri F, C. Guarneri, S. Benvenga. Helicobacter pylori and autoimmune pancreatitis: role of carbonic anhydrase via molecular mimicry. *J Cell Mol Med*, **9**, 2005 741-414
10. Hoshino C. Adult onset Schönlein-Henoch purpura associated with Helicobacter pylori infection. *Intern Med*, **48**, 2009, 847-51
11. Kanna, S. Free radical theory of autoimmunity. *Theoretical biology and medical modeling*, 2006, **3**, 22
12. Lahner E., B. Annibale. Pernicious anemia: New insights from a gastroenterological point of view. *World J Gastroenterol*, **15**, 2009, 5121-5128
13. Luther J, M. Dave, P. Higgins et al. Association between Helicobacter pylori infection and inflammatory bowel disease: A meta-analysis and systematic review of the literature. *Inflamm Bowel Dis.* 2009
14. Pietroiusti A., M. Giuliano, A. Magrini. Cytotoxin-Associated Gene A Strains of Helicobacter Pylori Represent a Risk Factor for the Development of Microalbuminuria in Type 2 Diabetes. *Diabetes Care*, **29**, 2006, 1399-1401
15. Song M., D. Park, S. Hwang. The Prevalence of Helicobacter pylori Infection in Korean Patients with Inflammatory Bowel Disease, a Multicenter Study. *Korean J Gastroenterol.* **53**(6), 2009, 341-347.
16. Suzuki1 H., B. Marshall. Helicobacter pylori: present status and future prospects in Japan. *J Gastroenterol*, **42**, 2007, 1-15
17. Tomasi P., M. Dore, G. Fanciulli et al. Is there anything to the reported association between Helicobacter pylori infection and autoimmune thyroiditis. *Dig Dis Sci*, **50**, 2005, 385-8
18. Tsang K., S. Lam. Extragastroduodenal conditions associated with Helicobacter pylori infection. *HKMJ*, **5**, 1999, 169-174