# EDITORIAL

## IS *HELICOBACTER PYLORI* RESPONSIBLE FOR AUTOIMMUNE DISEASES? THAT IS THE QUESTION

*Defense against infectious agents and other external aggressions is guaranteed by a complex immune system in which the lymphocytes are the main protective elements – with the mission of identifying the foreign antigens pertaining to the exogenous agents, and of producing specific antibodies against them, while at the same time recognizing as own all the endogenous substances produced by the human body. Primary failure of these defense mechanisms gives rise to a broad range of disorders (primary immune deficiencies), the main origin of which is represented by genetic defects that are increasingly better identified and related to each of these diseases[1]. Secondary immune deficiencies in turn appear late, in the course of many serious illnesses, in which the associated deterioration also affects the host immune system. This situation is generally taken advantage of by the so-called opportunistic microorganisms[2]. Another example of secondary immune deficiency is that associated with HIV infection, characterized by well known alterations in the patient immune response.*

*Separate mention must be made of those diseases that develop as a result of failure to recognize the body components as own – thus resulting in the generation of autoantibodies that ultimately cause tissue damage. The consequence of such situations is the development of autoimmune pathology, with etiopathogenic features that have not been fully clarified, though both environmental and genetic factors (particularly relating to the major histocompatibility complex (MHC) genotype) are clearly significant[3]. Naïve lymphocytes can react with autoantigens, thereby triggering the mechanisms that activate the T and/or B lymphocytes[4]. At present, a new factor has been related to autoimmune pathology – particularly rheumatoid arthritis and multiple sclerosis. This new factor is represented by the so-called Th17 lymphocytes, which are different from the Th1 and Th2 cells, and which produce interleukin 17 (IL-17). The latter in turn appears to be implicated in the pathogenesis of such diseases[5].*

*At present, the participation of two additional factors in autoimmune processes is being debated. In effect, TNF-alpha and possibly also other cytokines related with it are implicated at least in perpetuation of the inflammatory cascade. Specific block of this factor has been effective in reducing the symptoms of rheumatoid arthritis and perhaps also systemic lupus erythematosus[6]. In contrast, interferon-beta type 1 (T1IFN-β), the first choice treatment for multiple sclerosis with the main function of promoting innate immunity, could prevent the progression of some autoimmune disorders, since it promotes the production of a series of cytokines (IL-4, IL-5 and IFN-γ)[7].*

*There is controversy regarding the role which infection caused by certain germs might play in the induction of autoimmune diseases – despite the fact that such an association has been observed in a good number of cases, such as for example in reactive arthritis following infection by different strains of* Shigella, Salmonella *or* Yersinia, *or in rheumatic fever secondary to* Streptococcus A *when the patient carries the aforementioned genetic predisposing factors (MHC genotype)[3]. At present, special mention also should be made of* Helicobacter pylori *(HP), which may be responsible for another range of disorders (chronic urticaria, vascular diseases, etc.)[8,9].*

*First identified in Australia in 1983, HP is a gramnegative bacterium found in a large proportion of the healthy population, though its prevalence has been associated with lower socioeconomic levels – affecting an estimated 13-70 % of individuals under 20 years of age. This figure reaches 94 % in older age groups, and is considerably lower in the more developed parts of the world. Since its discovery, this bacterium has been related to gastrointestinal disorders (gastritis and ulcers), produced by autoantibody action, and which in susceptible individuals could constitute the basis for other autoimmune disorders[10-12], in addition to the risk of gastric neoplastic processes over the long term.*

*It is currently debated whether HP is related to other generalized autoimmune processes (both systemic and organ-specific) following gastric atrophy as a first step in the production of autoantibodies against the proprietary host antigens. Among the different related disease processes (hepatitis, pancreatitis, neutropenia), the most notorious may be pernicious (megaloblastic) anemia, thrombocytopenic purpura and autoimmune thyroiditis (Graves' disease and Hashimoto's disease) – the possible inclusion of Sjögren's syndrome and rheumatoid arthritis being the subject of debate.*

Pernicious anemia *is associated with atrophy of the gastric body secondary to an autoimmune process. The most significant feature is the lack of vitamin B12 (cobalamin) absorption due to the absence of intrinsic factor within the gastric mucosa. Among other authors, Annibale et al.[13] have found HP in 60 % of the patients with pernicious anemia, with the presence of functional and histological alterations. Similar results have been reported by Serin et al.[14], though a more significant observation is the clinical improvement and increase in serum cobalamin levels recorded by Kaptan et al.[15] in patients after the eradication of HP.*

*Different studies have reported the presence of HP in patients with* thrombocytopenic purpura*, though the pathogenic relationship in this case has not been well established, and there are evident differences from one country to another. The efficacy of eradication of the microorganism is controversial (Kuwana et al.[16]), despite the fact that some studies have published increases in platelet count after eradication[17,18].*

*A large percentage of patients with* autoimmune thyroiditis *are infected with HP. In this sense, it has been suggested that monoclonal antibodies targeted against CagA+ strains (the most pathogenic) may exhibit cross-reactivity with the thyroid follicular cells[19]. Moreover, in these patients there have been reports of high titers of antimicrosomal and antithyroglobulin antibodies[20]. Both observations appear to correlate the infection to the pa-*

*thogenesis of thyroiditis, though there are no conclusive studies in this sense. Larizza et al. have suggested the eradication of HP in children with autoimmune thyroiditis and susceptible HLA alleles, and even in those with the these alleles but who have not yet developed the disease – in view of the risk of developing the latter over the long term*[21].

*Another two autoimmune processes,* Sjögren's syndrome *and* rheumatoid arthritis*, have been the subject of different studies, in an attempt to determine the implication of HP in the pathogenesis of these two disorders, and the eradication of the germ as a possible treatment option. The results to date are contradictory and not definitive. As a result, and for the time being, anti-infectious treatment does not seem indicated in daily clinical practice – though further studies are needed in this field*[22-25].

*In sum, the participation of* Helicobacter pylori *in the etiopathogenesis of autoimmune processes is subject to controversy, though eradication of the germ proves promising in some cases – particularly among genetically susceptible patients (MHC), in whom the development of a disorder of this kind could even be avoided provided treatment is administered as soon as the presence of the bacterium in the stomach is detected*[3,26].

***F. Muñoz-López***

## References


1. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol. 2007;120:776-94.
2. Muñoz-López F. Inmunodeficiencias secundarias en el niño. Pediatría Integral. 1999;4:40-53.
3. Janeway CH, Travers P, Walport M, Shlomchik MJ. Inmunobiología. El sistema inmunitario en condiciones de salud y enfermedad. Ed. Masson, 2.ª ed., Barcelona, 3003.
4. Christen U, Herrath MG. Initiation of autoimmunity. Curr Opin Immunol 2004;16:759-67.
5. Furuzawa-Carballeda J, Vargas-Rojas MI, Cabral AR. Autoimmune inflammation from the Th17 perspective. Autoimmun Rev. 2007;6:169-75.
6. Lorenz HM, Herrmann M, Kalden JR. The pathogenesis of autoimmune diseases. Scand J Clin Lab Invest Suppl. 2001;235:16-26.
7. Gigli G, Caielli S, Cutuli D, Falcone M. Innate immunity modulates autoimmunity: type 1 interferon-β treatment in multiple sclerosis promotes growth and function of regulatory invariant natural killer cells through dendritic cell maduration. Immunology. 2007;122:409-17.
8. Muñoz-López F. *Helicobacter pylori* and allergic disease. Editorial. Allergol et Immunophatol. 2003;31: 253-5.
9. Martín de Argila C, Boixeda D. Manifestaciones extradigestivas de la infección por *Helicobacter pylori*. ¿Ciencia o ficción? Med Clinica. 2000;114:308-17.
10. Presotto F, Sabini B, Cecchetto A, Plebani M, De Lazzari F, Pedini F et al. *Helicobacter pylori* infection and gastric autoimmune diseases: is there a link? Helicobacter. 2003;8:578-84.
11. Bergmann MP, Vandenbroucke-Grauls CM, Appelmelk BJ, D'Elios MM, Amedei A, Azzurri A et al. The story so far: *Helicobacter pylori* and gastric autoimmunity. Int Rev Immunol. 2005;24:63-91.
12. Bergman M, Del Prete G, van Kooyk Y, Appelmelk B. *Helicobacter pylori* phase variation, immune modulation and gastric autoimmunity. Nature Reviews. Microbiology. 2006;4:151-9.
13. Annibale B, Lahner E, Bordi C, Martino G, Caruana P, Grossi C et al. Role of *Helicobacter pylori* infection in pernicious anaemia. Dig Liver Dis. 2000;32:756-62.

14. Serin E, Gümürdülü Y, Ozer B, Kayaselçuk F, Yilmaz U, Koçac R. Impact of *Helicobacter pylori* on the development of vitamin B12 deficiency in the absence of gastric atrophy. Helicobacter. 2002;7:337-41.
15. Kaptan K, Beyan C, Ural AU, Cetin T, Avcu F, Gülçen M et al. *Helicobacter pylori*—is it a novel causative agent in vitamin B12 deficiency? Arch Inter Med. 2000;160:1349-53.
16. Kuwana M, Ikeda Y. *Helicobacter pylori* and immune thrombocytopenic purpura: unsolved questions and controversies. Int J Hematol. 2006;84:309-15.
17. Sato R, Murakami K, Watanabe K, Okimoto T, Miyajima H, Ogata M et al. Effectc of *Helicobacter pylori* eradication on platelet recovery in patients with chronic idiopathic thrombocytopenic purpura. Arch Inter Med. 2004;164:1904-7.
18. Campuzano-Maya G. Proof of an association between *Helicobacter pylori* and idiopathic thrombocytopenic purpura in Latin America. Helicobacter. 2007;12:265-73.
19. Tomasi PA, Dore MP, Fan ciulli G, Sanciu F, Realdi G, Delitala G. Is there anything to the reported association between *Helicobacter pylori* infectkion and autoimmune thyroiditis? Dig Dis Sci. 2005;50:385-8.
20. De Luis DA, Varela C, de La Calle H, Cantón R, de Arguila CM, San Román AL et al. *Helicobacter pylori* infection is markedly increased in patients with autoimmune thyroiditis. J Clin Gastroenterol. 1998;26: 259-63.
21. Larizza D, Calcaterra V, Martinetti M, Negrini R, De Silvestri A, Cisternino M et al. *Helicobacter pylori* infection and autoimmune thyroid disease in young patients: the disadvantage of carrying the human leukocyte antigen-DRB1*0301 allele. J Clin Endocrinol Metab. 2006;91:176-9.
22. Theander E, Nilsson I, Manthorpe R, Jacobson LT, Wadström T. Seroprevalence of *Helicobacter pylori* in primary Sjögren's syndrome. Clin Exp Rheumatol. 2001;19:633-8.
23. El Miedany YM, Baddour M, Ahmed I, Fahmy H. Sjögren's syndrome: concomitant *H. pylori* infection and possible correlation with clinical parameters. Joint Bone Spine. 2005;72:135-41.
24. Zentilin P, Seriolo B, Dulbecco P, Caratto E, Iiritano E, Fasciolo D et al. Eradication of *Helicobacter pylori* may reduce disease severity in rheumatoid arthritis. Aliment Pharmacol Ther. 2002;16:1291-9.
25. Tanaka E, Kamitsuji S, Inoue E, Yamada T, Nakajima A, Takeuchi E et al. Nonsteroidal anti-inflammatory drug use not affect short-term Endoscopic and histologic outcomes after *Helicobacter pylori* eradication in patients with rheumatoid arthritis. Mod Rheumatol. 2007;17:228-34.
26. Dore MP, Fastame L, Tocco A, Negrini R, Delitala G, Realdi G. Immunity markers in patients with *Helicobacter pylori* infection: effect of eradication. Helicobacter. 2005;10:391-7.