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Vincenzo Bassi[1]*, Olimpia Fattoruso[2] and Crescenzo Santinelli[1]

[1]U.O.C. di Medicina Interna e di Urgenza, S Giovanni Bosco Hospital, ASL Na-1 Centro, Naples, Italy
[2]U.O.C di Patologia Generale, S Giovanni Bosco Hospital, ASL Na-1 Centro, Naples, Italy

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***Corresponding author:** Vincenzo Bassi, UOC of Internal Medicine, S Giovanni Bosco Hospital, ASL Na-1 Center, Naples, Italy, Tel.: +39390815562981; Fax: +39390815562981: E-Mail: dr_bassi@inwind.it

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Mini Review

Autoimmune Thyroid Diseases and Helicobacter Pylori

Abstract

Background: Helicobacter pylori infection is worldwide diffused with up to 50% of incidence in the population of the developed countries and the most virulent strains carrying the cytotoxin-associated gene A antigens. Moreover, bacterial and viral antigens have been suspected to be able to mimic the antigenic profile of the thyroid cell membrane suggesting an important role in the onset of the autoimmune diseases, such as Graves' disease and Hashimoto's thyroiditis. Aims: we reviewed the studies concerning the relationship between the bacterium and the autoimmune thyroid diseases such as Graves' and Hashimoto's disease. Conclusions: the significative association between Helicobacter pylori and Graves' disease suggests a possible role of this bacterium in the onset and/or the maintenance of the autoimmune disease.

Review

Helicobacter pylori (H. pylori) infection is worldwide spread with an incidence up to 50% of the population in developed countries and 80% in developing countries [1]. The prevalence rate of the infection shows a cohort effect and an increased rate usually is found in elders and males in Italy [2]. The bacterium is a motile, gram-negative microrganism, which typically colonizes the gastric mucosa; serologically it is possible to identify the most virulent strains by the presence of the cytotoxin-associated gene A (Cag-A) antigen [3]. The bacterium is responsible of gastric diseases such as gastritis, gastric/duodenal ulcers and carcinomas [4]. Moreover, extra-digestive diseases, such as immune thrombocytopenic purpura and coronary heart disease, have been reported to be strictly associated with H. pylori [5].

The autoimmune Thyroid Diseases (ATDs) are represented, essentially, by Hashimoto's Thyroiditis (HT) and its variants (postpartum and sporadic thyroiditis), Graves'Disease (GD) and athrophic thyroiditis [6]. These diseases show a typical marker in the presence of autoantibodies against thyroglobulin (TgAbs), thyreoperoxidase (TPOAbs) and thyrotropin receptor (TRAbs). Both genetic and environmental factors are implicated in the pathogenesis of ATDs and some bacteria and viruses have been suspected to be able to mimic the antigenic profile on thyroid cell membrane, suggesting an important role in the onset of the autoimmune diseases [7]. Furthermore, increased levels of antibodies against some bacteria antigens have been found in the serum of GD patients [8] and, moreover, many gram-positive and gram-negative bacteria show an antigen structure similar to a TSH-binding protein [9].

In the past years different studies have shown a significative correlation between H. pylori presence and HT, although others deny such association [10-16]. The use of different techniques to identify H. pylori infection could explain these conflicting conclusions. For instance, serological detection of H. pylori antibodies is not useful to discriminate between past and ongoing infections. Conversely, ^{13}C-urea breath test and immunoassay test on fresh stool samples detect only ongoing H. pylori infections and are currently considered the preferred not-invasive methods of investigation [17]. Moreover, the presence of similar antigenic sites between a bacterial antigen, such as Cag-A, and TPO structures explains the false positivity of the Abs titers against H. pylori, suggesting a possible bias in the group selection of the enrolled patients in some studies [18]. Also, the different grade of thyroid hypofunction, such as the subclinical or frank hypothyroidism, in the group of HT patients, could be a misleading factor.

Recently, a noteworthy correlation has been demonstrated between an overall H. pylori infection and GD, independently of the hormonal status, using a stool antigen test [19]. Moreover, the correlation with H. pylori has been demonstrated only in hyperthyroid GD patients but not in frank hypothyroid HT patients while, conversely, the Cag-A carrier strains of the bacterium seems to correlate with both thyroid diseases [20]. Furthermore, a recent study showed an increased rate of H.

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pylori recurrence in GD patients occurring in a short time span, six and twelve months, after successful drug eradication [21]. Suggesting that the H. pylori recrudescence seems to be the more logical explanation vs. a true reinfection of a different bacterium strain. In the future studies of molecular fingerprinting techniques of the involved strains could be useful to clear this hypothesis.

Several factors could be considered to explain the different observed results of H. pylori prevalence in GD and HT. Usually, the onset of different ATDs is dependent on numerous autoimmune mechanisms. Cellular autoimmunity with T-Helper (TH) 1 profile of CD4+T helper precursor cells is usually predominant in HT, whereas humoral autoimmunity, expressing in the production of TRAbs or TSH-receptor blocking antibodies, is associated with TH2 profile, prevalent in GD and atrophic thyroiditis. The activated TH profiles induce the expression of different panels of cytokines, such as tumor necrosis factor-alpha (TNF-a), interleukin (IL)-2 and interferon-gamma in HT and IL-4, IL-5, IL-6, IL-9. IL-10 and IL-13 in GD [22]. Moreover, the H. pylori infected patients show a TH2 polarization associated to a TH1 marked reduction suggesting a strong predisposition to humoral autoimmunity onset [23].

Also, the thyroid function, hyperthyroidism vs. hypothyroidism, could be another factor leading to the controversial results on H. pylori prevalence in GD and HT patients.

Anyway, the suggested factors could play through a common pathway, such as the glycoconjugates-mediated adhesion of H. pylori to the gastric mucosa, a crucial step in the establishment of successful bacterial infection. H. pylori glycan receptors include fucosylated ABO blood group antigens and glycans with charged groups, such as sialic acid or sulfate, and neolacto core chains [24-26]. Many H. pylori adhesins have been identified on the basis of their interactions with these receptors: the blood group antigen-binding adhesion (BabA) is specific for H type-1 and Lewis-b antigens, admitting terminal blood groups A and B glycan determinants, whereas the Sialic Acid Binding Adhesin (SabA) recognizes the Sialyl-Lewis a and Sialyl-Lewis x antigens [27-29].

Then, factors such as hyperthyroidism and/or different cytokines induced by humoral immunity, could modify the profile of the adhesion molecules expressed on the gastric mucosa, increasing the overall H. pylori binding in GD and selecting the prevalent Cag-A positive strains in ATDs.

In conclusion, it is possible to suggest a "trigger" role of H. pylori in the onset/maintainance of ATDs?

The increased positivity of H. pylori in GD, upon Vfirst diagnosis, and the previous observation that H. pylori infection, usually, starts during childhood [30], suggest that the bacterium is present before the onset of the autoimmune disease. Larizza et al. have proposed that H. pylori infection can induce and/or worsen the course of GD in susceptible young patients showing the human leukocyte DRB1*0301 antigen profile [31]. Then, the authors suggested that H. pylori eradication could prevent GD in these "at high risk" children. Moreover, Cag-A positive H. pylori strains show some nucleotide sequence similarity to thyroid peroxidase (TPO) sequence [32] and a positive linear regression between H. pylori-Abs titers and microsomial autoantibodies with a significant reduction of these antibodies after H. pylori eradication have been demonstrated [33]. Then, cross-reactivity of the antibodies produced against thyroid antigen structures during H. pylori infections could induce a biological effect (Figure 1).

Conversely, hyperthyroidism in GD patients could just be a predisposing factor to H. pylori infection, and the gastric colonization of the microorganism could represent an epiphenomenon, not involved in the onset of the autoimmune disease (Table 1).

In conclusion, further studies will be necessary to investigate the correlations between the bacterium and ATDs but the demonstrated increased infection rate of H. pylori in ATDs suggests that it is possible in the future to add new findings in the puzzling factors underlying the mechanism of ATDs onset.

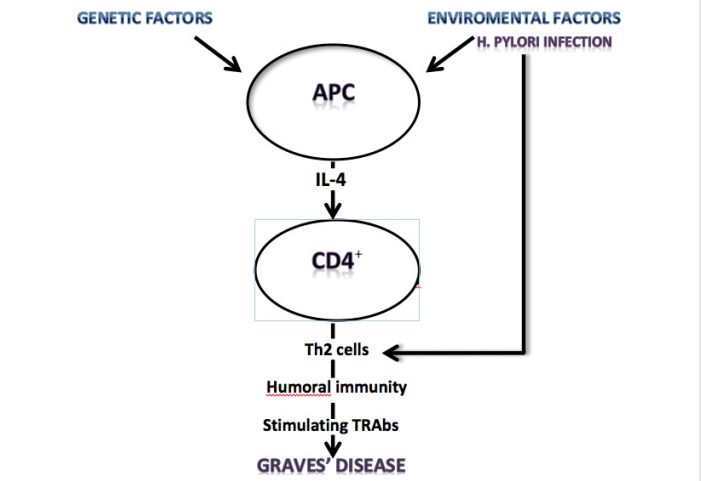

Figure 1: Genetic and environmental factors involved in the pathogenesis of Graves' disease. The Helicobacter pylori role is showed in the Graves'Disease onset.

Table 1: Evidences in support or against the H. pylori role in the Graves' disease

Evidences
In support
• Antigens similarity between TPO and H. pylori structures (inducing cross reacting antibodies) have been demonstrated
• Onset of H. pylori infection is present in childhood and the infection is usually found at the first diagnosis of GD
• Some HLA II alleles found in GD patients are frequently associated with H. pylori infection
• H. pylori is able to induce a systemic Th-2 induction, usually described in GD patients
Against
• Increased rate of H. pylori recurrence is observed after drug eradication (GD-induced susceptibility to the bacterium infection?)

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