

The Association of *Helicobacter pylori* Infection with Hashimoto's Thyroiditis

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Abstract- Autoimmune thyroid diseases (ATD) are multifactorial conditions that result from genetic predisposition in combination with environmental risk factors. *Helicobacter pylori* infection as an environmental risk factor has been proposed to imitate the antigenic components of the thyroid cell membrane and may play a leading role in the onset of the autoimmune diseases, such as Hashimoto thyroiditis. The aim of this study was to investigate the association between *Helicobacter pylori* (HP) infection and Hashimoto's thyroiditis (HT). The participants in this case-control study included 43 patients affected by Hashimoto's thyroiditis, and 40 healthy individuals without history of autoimmune disease as the control group. Anti HP IgG and anti-TPO antibodies were determined using ELISA method. Results were considered positive when the IgG anti-HP value was higher than 30 IU/ml and the anti-TPO autoantibody value was higher than 75 IU/ml. The mean TSH level was 18.3 ± 16.8 IU/ml for patients and 2.8 ± 1.2 IU/ml for the control group ($P < 0.001$). 46.5% of the patient group and 10.8% of the control group were infected with HP. The association between HP and Hashimoto's thyroiditis was statistically significant (Odds Ratio=7.2, 95%, Confidence Interval: 2.0- 28.8, $P < 0.001$). The findings show that, there is an association between HP and Hashimoto's thyroiditis. To establish a definite correlation between them, more detailed studies with a more specialized examination and precise consideration regarding species of HP, genetic polymorphism of the host and investigation of environmental factors are needed.

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Introduction

Autoimmune thyroid diseases (ATD) are multifactorial conditions that result from genetic predisposition in combination with environmental risk factors (1). Regarding environmental risk factors, infectious agents such as *Helicobacter pylori* (HP), *Yersinia enterocolitica* and nutritional issues are believed to be involved (2). These diseases, despite their benign aspects have an unknown etiology that has not been cured yet; and the affected patients will be dealing with the symptoms, complications of disease and the side effects of the drugs for the rest of their life (2).

Helicobacter pylori infection as an environmental

risk factor has been suspected to be able to mimic the antigenic profile of the thyroid cell membrane and to play an important role in the onset Hashimoto thyroiditis (3). HP is a labyrinthoid gram negative bacterium which is mostly found in mucus membranes in the stomach of an infected patient. HP is the most common bacterial infection among humans (4).

This organism is also seen in other diseases such as primary biliary cirrhosis (5), functional vascular disorders (primary migraine and primary Raynaud's phenomenon) (6,7), and ischemic heart disease (8-10).

Antibodies produced in reaction to HP antigens can cross-react with many normal tissue antigens of the human body, including thyroid tissue (11).

Researchers believe that HP is transmitted orally (12). In addition gastroesophageal reflux brings the bacteria into the mouth and targets the thyroid cells (13). According to the evidence suggesting the possible association of HP and ATD (11,14,15) and the speculation expressed in this issue (16,17), we decided to investigate the association between HP and Hashimoto's thyroiditis.

Materials and Methods

In this case-control study, participants included 43 patients affected by Hashimoto's thyroiditis in whom their disease was established according to clinical criteria (goiter), increased TSH, normal or low T4 and positive anti-thyroid peroxidase antibody (anti-TPO Ab), and 40 healthy individuals with no history of autoimmune disease as the control group. In the control group, those with goiter, positive anti-TPO Ab or high titer of TSH were not included. In addition, subjects who had prior history of thyroid surgery, taking radioactive iodine, dyspepsia, peptic ulcer or treatment for HP were excluded from the study. All eligible participants signed a written consent form.

Sufficient venous blood (about 5 ml) was sampled for measuring anti-HP IgG Ab, TSH and anti-TPO Ab from both groups. Anti-HP IgG Ab was measured by ELISA method using a Radium-DRG kit and its titer of more than 30 IU/ml was considered as positive. Serum anti-TPO Ab was also measured by the ELISA method using a Genesis kit and levels more than 75 IU/ml were supposed positive. The serum TSH was assessed by the ELISA method using a Diaplus kit, and values more than 5 IU/ml were considered positive.

Statistical analysis

Kolmogrov-Smirnov, independent t-test, Chi-Square, Odds Ratio (OR) and 95% Confidence Interval (CI) tests were used for the statistical evaluation of the data.

$P < 0.05$ was considered as statistically significant.

Results

In this study, 43 patients were affected by Hashimoto's thyroiditis and 40 individuals formed the control group but three individuals from the control group were excluded; two subjects because of a positive anti-TPO Ab and one due to a high level of TSH.

In respect to gender, both groups were identical ($P = 0.757$). 16.3% of the patients and 18.9% of the control group were male. The mean age (\pm SD) of the patients was 34.4 ± 11.1 for the case group and 34.8 ± 7.8 for the control group ($P = 0.851$).

The mean TSH level was 18.3 ± 16.8 IU/ml for patients and 2.8 ± 1.2 IU/ml for the control group ($P < 0.001$).

The results showed that anti-HP IgG Ab was positive in 46.5% of patients compared to 10.8% of the subjects in the control group, indicating an association between HP infection and Hashimoto's thyroiditis (OR=7.2, 95% Confidence Interval: 2.0-28.8, $P < 0.001$). Table 1 shows clinical and biochemical parameters of the study subjects.

Discussion

The findings in this study showed a significant association between Hashimoto's thyroiditis and HP infection.

In a study conducted by Larizza *et al.* (14), HP was proposed as one of the etiologic causes of thyroid autoimmune disease. Bertolat *et al.* (15) showed that individuals with a high titer of Anti-TPO Ab were significantly affected by HP infection and eradication of HP causes a significant reduction in Anti-TPO Ab and Anti-thyroglobulin.

Table 1. Clinical and Biochemical Parameters of the study subjects.

Parameter	Case (n=43)	Control (n=37)	P-value
Age	34.4 ± 11.1	34.8 ± 7.8	0.851
Gender (male)	16.3%	18.9%	0.757
TSH level (IU/ml)	18.3 ± 16.8	2.8 ± 1.2	0.0009
Anti HP IgG Ab (+)	46.5%	10.8%	0.0008

Data are expressed as mean \pm standard deviation, numbers or percentages.

TSH; Thyroid Stimulating Hormone

HP; Helicobacter Pylori

IgG; Immunoglobulin G

Ab; Antibody

De Luis *et al.* (11) showed that the titer of Anti-HP IgG Ab in Graves' and Hashimoto's thyroiditis was much higher compared to the control group. Figura *et al.* (18) also found a significant correlation between HP+Cag A and autoimmune thyroid disease. Sterzl *et al.* (19) showed a significant association between positive Anti-HP Ab and ATD. In another study conducted by Bures *et al.* (20), the level of Anti-TPO Ab was higher in HP positive than in HP negative patients. In another study Tomasi *et al.* (16) investigated the relationship between HP infection and ATD. 302 patients with signs and symptoms of dyspepsia underwent an upper endoscopy and patients were evaluated for HP infection and autoimmune thyroid disorders. In this study, 36.8% of the individuals were positive for HP. The concentrations of serum Anti-TPO and Anti-TG Abs in both groups were identical and no hormonal differences were observed in patients with or without HP. In this study, there was no significant association between HP infection and increased risk of ATD in patients with symptoms of dyspepsia. In this study, the dyspeptic patients were first selected based on their HP positivity and then autoimmune thyroiditis were investigated, which is substantially different from the method of our study.

Based on the previous studies, 80% of the population in developing countries will have HP infection but only 10 to 15% of the individuals will have a frank peptic ulcer (21). The reality is that, if this study could be performed in a population affected by gastric ulcers, 30-60% would be positive for HP and in a population with duodenal ulcers, 50-70% would be positive. HP could be the cause of many digestive and non-digestive diseases in humans; one of them with a low percentage of probability could be thyroid autoimmune disease. As all patients affected by HP do not show clinical signs of the disease, the estimation of this disease requires a bigger population of patients affected by ATD; so, it seems that the above mentioned study cannot give an appropriate answer to the question; therefore, to postulate a hypothesis that HP could be a probable cause of ATD, it would be better to select patients affected by ATD.

In the other study conducted on 20 patients and 20 normal people by Franceschi *et al.* (17), the prevalence of HP infection in the patients and the control group were the same and based on these findings they deduced that a relation between HP infection and Hashimoto's thyroiditis was unlikely. It seems that the limited sample size of this study was the cause of the negative outcomes.

As the fetal origin of the thyroid gland is the same as

the stomach and digestive tract, we can consider thyroid cells as a digestive tract cell, capable of accumulating, concentrating and combining iodine compounds. Both thyroid and the stomach have the ability to concentrate iodine. In addition, in terms of cell polarity, the presence of apical microvilli, synthesis and excretion of glycoprotein (thyroglobulin and mucin) they are alike. Superficial parietal cell antigens of the stomach are homologous with protein portion of thyroid peroxidase enzyme. Fetal and structural similarity of these two organs may justify their simultaneous involvement in some diseases and it is realized that HP infection could trigger the mechanism of autoimmune reaction such as increased thyroid antibodies (22).

In general, most individuals who are colonized with HP do not show a clinical sequel of the infection. This is probably due to a combination of different species of the bacteria, sensitivity, genetically polymorphism of the host and environmental factors; virulence of HP is the most important factor (20).

Ultimately, although the present study demonstrates the association between HP and Hashimoto's thyroiditis, more detailed researches with a more specialized examination and precise consideration of HP species, genetic polymorphism of the host and investigation of environmental factors are needed.

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