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Correlation between Autoimmune Thyroid Diseases and Helicobacter Pylori Infection

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ABSTRACT

Background: Helicobacter Pylori (H. Pylori) usually acquired in childhood, it colonizes the gastric mucosa of about 50% of the world's population at some time in their life. In eastern countries, H. pylori infection has a prevalence of approximately 70%. **Objective:** To correlate between H. pylori infection and autoimmune thyroid diseases (AITD).

Patients and Methods: This is a cross-sectional study done on 200 patients selected as a convenient sample with upper GI upset. They were selected from gastroenterology outpatient clinics at Al-Hussein and Alexandria Police Hospitals, during the summer months of 2018. They were classified according to the results of stool H. pylori Ag testing into two groups; positive and negative (each group 100 patient).

This is cross-sectional study done on 200 patients selected as a convenient sample

Results: Our results indicated that patients with H. pylori infection were more susceptible to AITD. There was significant association between H. pylori infection and both Hashimoto's and Graves' disease. H. pylori infection had shown to be associated with elevated liver enzymes, anemia, and IL 17.

Conclusion: There is a significant positive relationship between H. pylori infection and Hashimoto's disease (HT). There is a significant positive relationship between H. pylori infection and Graves' disease (GD).

Keywords: Autoimmune Thyroid Diseases, Helicobacter Pylori.

INTRODUCTION

Helicobacter pylori (H. pylori) infection is confirmed to correlate with chronic gastritis, peptic ulcer disease, mucosa associated lymphoid tissue (MALT)-lymphoma, precancerous changes in the stomach (atrophy, intestinal metaplasia), and gastric cancer [(1)].

At the same time, H. pylori eludes the immunological response evoked by the host. H. pylori have acquired several abilities that help them to escape clearance through the host immune system. Then H. pylori interact with the immune system [(2)].

Autoimmune diseases are characterized by dysregulation of the immune system resulting in a loss of tolerance to self-antigen. The exact etiology for the majority of these diseases is unknown; however, a complex combination of host and environmental factors are believed to play a pivotal role. Numerous pathogens were implicated as possible environmental agents contributing to the development of autoimmune disease in susceptible individuals. Polyclonal lymphocyte activation, molecular antigen mimicry, epitope spreading, bystander activation, and activation by a super-antigen, were all proposed as possible mechanistic links between the development of autoimmunity and exposure to infectious agents. Discussion of these mechanisms was previously detailed in the medical literature. In their review of the role of infectious agents in autoimmunity, Getts et al., suggested that autoimmune disease is triggered by these mechanisms working 'simultaneously and/or sequentially' [(3)].

Evidence for the role of infectious agents in diseases such as rheumatic fever and Guillain-Barre syndrome is convincing [(4)]. However, evidence for the involvement of infectious agents in other autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) remains controversial. Chronic infection with H. pylori serves as a source of persistent antigenic stimulation and underlies the pathogens' ability to induce a systemic inflammatory response [(5)].

The prolonged interaction between the bacterium and host immune mechanisms makes H. pylori a plausible infectious agent for triggering autoimmunity. Molecular mimicry of H. pylori antigens was found to activate cross-reactive T cells which may lead to autoimmune gastritis [(6)].

Autoantibodies, such as IgM rheumatoid factor, anti-single stranded DNA antibody and anti-phosphotidyl choline antibodies, were demonstrated to be produced by B cells after their activation by H. pylori components, particularly urease [(7)].

A role of microbial heat shock proteins (HSP) in the pathogenesis of autoimmune diseases has been postulated because of the high level of sequence homology with human HSP. A possible role of HSP 60 produced by H. pylori in pathogenesis of Sjögren's syndrome is proposed [(8)].

Eradication of H. pylori infection in patients with immune thrombocytopenic purpura (ITP) was shown to be effective in improving platelet counts in 50% of cases [(9)].

Cross-reactivity between bacterial and thyroid antigens was proposed as a mechanism in H. pylori induced AiTD [(10)].

Indeed, amino acid sequence similarities between CagA H. pylori and thyroid peroxidase were

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reported, and one group described a reduction in thyroid autoantibodies following H. pylori eradication [(11)]. Larizza et al., suggests that H. pylori may induce or worsen Graves' disease in patients carrying HLADRB10301, and further suggested eradication in certain risk groups [(12)].

These findings do suggest a possible causative link between the CagA strain of H. pylori and the development of Graves' disease, but deserve further research. It should be noted that AITDs are often found concomitantly with other autoimmune conditions, and that the link between the pathogen and autoimmune disorders. GD diagnosis was defined by hormonal hyperthyroidism (suppressed TSH, elevated FT3 and FT4 and positive titres of TPOAbs, TgAbs, TRAbs [(13)].

AIM OF THE STUDY

To correlate between H. pylori infection and autoimmune thyroid diseases.

PATIENTS AND METHODS

This is cross-sectional study done on 200 patients selected as a convenient sample with upper GI upset. They were selected from gastroenterology outpatient clinics at Al-Hussein and Alexandria Police Hospitals, during the summer months of 2018.

They were classified according to the results of stool H. pylori Ag testing into two groups (each group 100 patient);

Group A: 100 patients with positive H. pylori Ag in the stool.

Group B: 100 patients with negative H. pylori Ag in the stool.

Ethical consideration and Written informed consent:

An approval of the study was obtained from Al-Azhar University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation.

All patients were submitted to full medical history and medical examination including stigmata of thyroid diseases.

All participants were subjected to the following nvestigations:

1- H. pylori Ab.
2-Thyroid perocxidase antibodies.
3- Thyroglobulin antibodies.
4-Thyrotropin antibodies.
5-Thyroid stimulating hormone.
6-FreeT3.
7-FreeT4.
8-C.B.C.
9-C.R.P.
10-Liver function testes (SGPT, SGOT, S. Albumen).
11-Kidney function testes (Urea, Creatinine, Uric Acid).
12-Interleukin 17.
13-Thyroid ultrasound.

Sample preparation:

- Blood was collected by venipuncture under complete aseptic conditions and then divided into 3 portions; 5 ml for serum separation in vacutainer tube, 3 ml on EDTA coated tubes and 2 ml on fluoride coated tubes. Blood samples on plain tubes left to be clotted and then serum was separated by centrifugation at 3000 rpm for 10 minutes. Serum was separated and divided into separate aliquots for immediate assays or frozen at -20° until assays were performed.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:

- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

Table (1): Comparison between groups A and B as regarding thyroid Ab titres

		Range	Mean ± S. D	t. test	p. value
Tg Ab (ug/L)	Group A	1.9 – 11.5	4.81 ± 2.14	24.307	0.001*
	Group B	1 – 11	3.53 ± 1.47		
TPO	Group A	0.5 – 17.9	8.27 ± 3.05	17.425	0.001*
	Group B	1 – 17	6.57 ± 2.72		
Thyrotrobin Ab	Group A	0.3 – 12	2.88 ± 2.96	19.591	0.001*
	Group B	0.2 – 9.3	1.42 ± 1.46		

*** Significant p value < 0.05**

Significant difference between group A and group B regarding TgAb, TPO and Thyrotrobin Ab

Table (2): Comparison between groups A and B as regarding AITD

Auto immune Thyroid	Group A	Group B	Total

Hashimoto's		**N**	18	3	21
		%	18.0%	3.0%	10.5%
Graves'		**N**	17	4	21
		%	17.0%	4.0%	10.5%
Non		**N**	65	93	158
		%	65.0%	93.0%	79.0%
Total		**N**	100	100	200
		%	100.0%	100.0%	100.0%
Chi-square	**X^2**	**23.724**			
	P-value	**0.001***			

*** Significant p value < 0.05**

Significant difference between group A and group B regarding Autoimmune thyroid (AITD)

Table (3): Comparison between groups A and B as regarding H. pylori Ab.

H. Pylori Ab			**Group A**	**Group B**	**Total**
+ve		**N**	100	35	135
		%	100.0%	35.0%	67.5%
-ve		**N**	0	65	65
		%	.0%	65.0%	32.5%
Total		**N**	100	100	200
		%	100.0%	100.0%	100.0%
Chi-square	**X^2**	**96.296**			
	P-value	**0.001***			

*** Significant p value < 0.05**

Significant difference between group A and group B regarding H. Pylori Ab

Table (4): Comparison between groups A and B as regarding sex

Sex			**Group A**	**Group B**	**Total**
Male		**N**	50	50	100
		%	50.0%	50.0%	50.0%
Female		**N**	50	50	100
		%	50.0%	50.0%	50.0%
Total		**N**	100	100	200
		%	100.0%	100.0%	100.0%
Chi-square	**X^2**	**0.0**			
	P-value	**1.0**			

Non significant difference between group A and group B regarding sex

Table (5): Comparison betwee Hashimotos and Graves' regarding sex

Sex			**Hashimoto's**	**Graves'**	**Non**	**Total**
Male		**N**	7	10	83	100
		%	33.3%	47.6%	52.5%	50.0%
Female		**N**	14	11	75	100
		%	66.7%	52.4%	47.5%	50.0%
Total		**N**	21	21	158	200
		%	100.0%	100.0%	100.0%	100.0%
Chi-square	**X^2**	**2.786**				
	P-value	**0.243**				

Non significant difference between three groups regarding sex

Table (6): Hb concentration regarding sex:

	Range	Mean	±	S. D	t. test	p. value

Hb (g/dL)	Male	11.2	–	17.2	14.64	±	1.60	0.986	0.322
	Female	5	–	17.4	14.39	±	1.87		

Non significant difference between male and female regarding Hb

Table (7): CRP level according to sex:

		Mean	±	S. D	t. test	p. value
CRP (mg/L)	Male	7.14	±	1.00	1.663	0.199
	Female	7.68	±	1.92		

Non significant difference between male and female regarding CRP

Table (8): Comparison between both studied groups regarding all investigations

		Mean	±	S. D	t. test	p. value
TSH (mU/L)	Group A	3.32	±	0.82	0.902	0.343
	Group B	3.00	±	0.80		
FT3 (pmol/L)	Group A	3.48	±	0.39	0.070	0.791
	Group B	3.44	±	0.98		
FT4 (pmol/L)	Group A	1.50	±	0.096	0.736	0.392
	Group B	1.41	±	0.059		
Tg Ab (ug/L)	Group A	4.81	±	1.14	24.307	0.001*
	Group B	3.53	±	0.47		
TPO	Group A	8.27	±	2.05	17.425	0.001*
	Group B	6.57	±	1.72		
Thyrotrobin Ab	Group A	2.88	±	0.96	19.591	0.001*
	Group B	1.42	±	0.46		
SGPT (U/L)	Group A	40.94	±	0.75	12.670	0.001*
	Group B	31.93	±	4.49		
SGOT (U/L)	Group A	36.52	±	5.68	7.682	0.006*
	Group B	30.89	±	2.91		
Albumin (g/dL)	Group A	4.04	±	0.41	0.839	0.361
	Group B	4.10	±	0.47		
Urea (mg/dL)	Group A	17.14	±	2.63	0.100	0.752
	Group B	17.41	±	2.40		
Creat	Group A	1.08	±	0.27	2.039	0.155
	Group B	1.03	±	0.22		
Uric Acid (mg/dL)	Group A	6.08	±	1.09	7.686	0.006*
	Group B	6.91	±	1.18		
RBCs (mcL)	Group A	4.62	±	0.64	7.924	0.005*
	Group B	4.87	±	0.61		
WBCs (mcL)	Group A	8.88	±	1.53	11.206	0.001*
	Group B	7.67	±	1.59		
PLT	Group A	271.56	±	3.05	13.500	0.001*
	Group B	317.49	±	3.47		
Hb (g/dL)	Group A	14.20	±	1.90	6.722	0.010*
	Group B	14.83	±	1.50		
CRP (mg/L)	Group A	7.78	±	1.97	3.146	0.078
	Group B	7.04	±	1.93		
IL-17	Group A	1294.78	±	46.92	10.417	0.001*
	Group B	1057.23	±	92.51		

*** Significant p value < 0.05**

Table (9): Comparison between AITD and normal subjects regarding all investigations

		Mean	±	S. D	F. test	p. value		
CRP (mg/L)	**Hashimoto's**	10.67	±	1.96	16.964	0.001*	P1	0.001*
	Graves'	7.62	±	1.62			P2	0.001*
	Non	6.95	±	1.85			P3	0.296
WBCs (mcL)	**Hashimoto's**	11.20	±	1.37	17.992	0.001*	P1	0.001*
	Graves'	8.63	±	1.49			P2	0.001*
	Non	7.84	±	1.62			P3	0.160
Uric Acid (mg/dL)	**Hashimoto's**	5.24	±	0.96	8.419	0.001*	P1	0.814
	Graves'	5.40	±	1.32			P2	0.002*
	Non	6.81	±	1.27			P3	0.004*
RBCs (cells/mcL)	**Hashimoto's**	4.46	±	0.78	12.475	0.001*	P1	0.238
	Graves'	4.24	±	0.67			P2	0.005*
	Non	4.85	±	0.56			P3	0.001*
PLT	**Hashimoto's**	237.86	±	1.25	38.508	0.001*	P1	0.008*
	Graves'	173.29	±	7.38			P2	0.001*
	Non	318.17	±	3.13			P3	0.001*
Hb (g/dL)	**Hashimoto's**	13.14	±	1.69	28.930	0.001*	P1	0.361
	Graves'	12.71	±	2.20			P2	0.001*
	Non	14.94	±	1.40			P3	0.001*
IL-17	**Hashimoto's**	1821.38	±	18.84	28.916	0.001*	P1	0.013*
	Graves'	1457.62	±	29.78			P2	0.001*
	Non	1052.80	±	39.47			P3	0.001*
SGOT (U/L)	**Hashimoto's**	50.33	±	6.06	64.248	0.001*	P1	0.535
	Graves'	52.52	±	10.07			P2	0.001*
	Non	28.99	±	2.08			P3	0.001*
SGPT (U/L)	**Hashimoto's**	60.43	±	9.06	109.985	0.001*	P1	0.351
	Graves'	64.10	±	5.93			P2	0.001*
	Non	29.57	±	2.66			P3	0.001*

*** Significant p value < 0.05**

DISCUSSION

In our study there is a relation between H. pylori infection and Hashimoto's and Graves' disease. The subjects of all groups were chosen in the middle aged to avoid the influence of the age as a factor affecting the results.

Autoimmune thyroid diseases are familial autoimmune disorders that are more common in women than men. These diseases include Graves' disease (GD), Hashimoto's thyroiditis (HT), atrophic thyroiditis, and subacute lymphocytic thyroiditis (also known as postpartum thyroiditis (PPT), painless thyroiditis (PT), or silent thyroiditis (ST) [(14)]. The primary pathological features of autoimmune thyroid diseases are thyroid tissue infiltration of lymphocytes and thyroid dysfunction. Other typical hallmarks of these diseases are thyroid autoantibodies such as thyrotropin receptor antibody (TRAb), anti-thyroglobulin antibody (TGAb), and anti-thyroperoxidase antibody (TPOAb) [(15)]. The production of these autoantibodies can be attributed to both environmental and genetic factors [(16)]. Cross-reactive antigens can induce superantigen-activated polyclonal T cells, increase expression of human leukocyte antigen in thyroid tissue and promote other autoimmune tolerance responses [(17)].

Our study included cases of GD and HT but no cases of atrophic thyroiditis or subacute lymphocyte thyroiditis. Many studies were done about correlation between AITD and H. pylori infection. For example, 11 studies [(18, 19)] indicated that H. pylori infection was associated with AITD as we found in our study, while four studies [(20, 21)] showed no correlation between H. pylori infection and AITD.

Our results indicated that patients with H. pylori infection were more susceptible to AITD. HT in groub A was 18% and in groub B was 3% while GD in group A was 17% and groub B was 4%.

H. pylori infection could induce autoantibody damage to gastric epithelial cells, leading to gastric disease and antigenic antibody cross-reactions causing thyroid tissue damage [(22)].

Thus, HT are GD are expected to be associated with H. pylori infection. These studies suggest that H. pylori infection was associated with the pathogenesis and development of AITD. Ours did not report the association between atrophic thyroiditis and H. pylori infection, while the conclusions from other studies[(18, 21, 22)] are controversial. Due to the limited number of publications and limited data, the correlation between

atrophic thyroiditis and H. pylori infection was not analyzed here.

The previously reported association between autoimmune thyroiditis and H. pylori infection was not observed in the study of **Tomasi *et al.*** [23] who found that infection by H. pylori does not appear to increase the risk of autoimmune thyroiditis in individuals with dyspeptic symptoms.

In agreement with our results **Cammarota *et al.*** [24] found that there is increasing evidence for a link between H. pylori infection and the development lymphoid follicles in the gastric mucosa which are common in autoimmune thyroid disease.

In our study we found that there was no significant differenc between HT are GD regarding ATID antibodies. As Tg ab was 85.7% in HT and 80.9% in GD. TPO was 90.4% in HT and 85.7% in GD. Thyrotrobin Ab was 80.9% in HT and 100% in GD with p value 0.286, 0.831, 0.929 respectively.

Also, there was no significant p value between HT and GD regarding association with H. pylori infection. But there was a significant difference between HT and normal individuals as regarding thyroiod Ab with p value 0.001. Also there was a significant difference between GD and normal individuals as regarding thyroiod Ab with p value 0.001. This is in agreement with **Fröhlich and Wahl** [25].

In our study there was a significant association between IL 17 and AITD, which is in agreement with **Zake *et al.*** [26], with p value 0.001. There was also significant p value (0.013) between HT and GD.

In our study there was a significant association between Hb concentration and RBCs count with AITD, which is in agreement with **Dorgalaleh *et al.*** [27] with p value 0.001 and 0.001 respectively, with no significant p value between HT and GD.

In our study there was a significant association between WBCs count and with AITD, which is in agreement with **Hiromatsu *et al.*** [28] with p value 0.001, significant p value between HT and GD 0.001, but there was no significant p value between GD patients and normal individuals.

In our study there was a significant association between CRP with HT not GD with p value 0.001 and 0.296 respectively. This is against the results of **Pamukcu *et al.*** [29] who found that there was significant relation between both HT and GD regarding CRP, but there was significant p value between HT and GD (0.001) in our study.

In contrast to our study, **Shen *et al.*** [30] we didn't find a significant relationship between H. pylori and thyroid nodules with p value 0.149, nodules in group A is 23% but in group B is 15%.

In our study there was a significant association between IL 17 and H. pylori, which is in agreement with **Alvarez-Arellano *et al.*** [31] with p value 0.001.

In contrast to our study **Cincinelli *et al.*** [32] we didn't find a significant relationship between sex and AITD with p value 0.243, (HT in males 33.3% and in females 66.7% while GD in males 47.6% and in females 32.4%).

CONCLUSION

From our results we can conclude the following:

There is a significant positive relationship between H. pylori infection and Hashimoto's disease (HT). There is a significant positive relationship between H. pylori infection and Graves' disease (GD).

RECOMMENDATIONS

Training the parents, especially mothers and grandmothers, about sanitation rules besides reaching safe water supplies, participating in "screen/therapy/follow up for recurrence" programme in adults who have gastrointestinal problems should be crucial.

Washing hands thoroughly, eating food that is properly prepared and drinking water from a safe, clean source are important steps for preventing H. pylori infection in children

The best way to decrease the prevalence of H. pylori infection in children is to educate women about how to protect themselves and their offspring from H. pylori infection.

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