How to Cite:
Rashed, Y. K., Shattaf, A., Alteneiji, S., Alfardan, A., & Al Ali, A. A. (2022). Helicobacter pylori infection and celiac disease in children, what is the relationship?. *International Journal of Health Sciences*, *6*(S7), 4473–4481. Retrieved from https://sciencescholar.us/journal/index.php/ijhs/article/view/12914

Helicobacter pylori infection and celiac disease in children, what is the relationship?

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***Abstract*---**Background: Celiac disease (CD) is an autoimmune disease affecting the small intestine, triggered by gluten. The pathogenesis of CD has been well defined, and the increasing prevalence of this disease had led to studying several environmental risk factors that may trigger an autoimmune process in the small intestine. Infection is one of the most important factors that can trigger autoimmune processes. The researchers have studied the association between H. pylori infection and CD, the authors have reported conflicting results. Purpose: to study the association of H. pylori and celiac disease (CD) at the time of CD diagnosis in children. Patient and Methods: All patients in the study were subjected to full history taking, thorough clinical examination, and laboratory investigations including Anti-tissue transglutaminase antibodies (IgA), anti-endomysial (IgA EMA), Stool Ag for H. pylori, CLO test for H. pylori, Immunoglobulins level, Upper gastrointestinal endoscopy with multiple biopsies for histopathological examination. Results: Anti TTG

Manuscript submitted: 9 May 2022, Manuscript revised: 18 July 2022, Accepted for publication: 27 August 2022

Ig A and Endomysial Ab were positive in 49 patients, while one patient showed negative results. 7 patients (14%) had H. pylori infection while the remaining 43 patients (86%) were negative for H. pylori infection at the time of CD diagnosis. Conclusion: This study did not find a correlation between H. pylori infection and CD. However, further studies are needed to assess if H. pylori have a potential role in the pathogenesis of CD.

***Keywords*---**Celiac disease – H. pylori - Anti TTG Ig A - Endomysial Ab

Introduction

Celiac disease (CD) is a lifelong autoimmune disease associated with damage to intestinal cells that may develop in a genetically predisposed child when exposed to gliadin (a protein fragment found in wheat, barley, and rye). Villous atrophy in the duodenal and jejunal regions and an increase in the number of intraepithelial lymphocytes (IEL) are characteristic. *(1)*

Celiac disease can occur at any age, either during childhood or old age. It has two peaks; the first is within the first 2 years of life, and the second peak is seen in the second or third decade of life. The risk of celiac disease is higher in children with a family history of celiac patients, Down syndrome, type 1 diabetes mellitus (DM), autoimmune thyroiditis, selective immunoglobulin (Ig)A deficiency, Williams syndrome, and Turner syndrome. *(2)*

Helicobacter pylori (Hp) causes chronic gastritis and peptic ulcer disease, also responsible for certain cancers mostly beyond childhood as primary gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. Infected children may be asymptomatic. The relationship between H. pylori infection and the development of extra-gastrointestinal autoimmune disorders such as immune thrombocytopenic purpura, multiple sclerosis, autoimmune thyroid disease, and psoriasis, are well known. *(3)*

The pathogenesis of CD was established, but the increasing prevalence of CD had raised the role of several environmental factors that may trigger an autoimmune process in duodenal and jejunal mucosa. Infant feeding practices, rotavirus infections, elective cesarean sections, and perinatal exposure to bacterial microbiota modulate the risk of CD. *(4)*

Aim of the study: to study the association of H. pylori and celiac disease (CD) at the time of CD diagnosis in children.

Patients and methods

This study included 50 pediatric patients recently diagnosed with Celiac disease, their age ranges from 4 years to 13 years. 17 males and 33 females. The study started in January 2016 till August 2022 and included patients from Dubai Hospital and Al Qassimi Women and Children Hospital – Sharjah - UAE.

Inclusion criteria: Children recently diagnosed with Celiac disease, all investigations done at the time of diagnosis of Celiac disease.

Exclusion criteria: Children with other autoimmune diseases, those with only gastric or only duodenal biopsies, and Patients who had previously received H. pylori eradication treatment were also excluded.

All patients in the study were subjected to full history taking, and a thorough clinical examination, laboratory investigations included full blood count (FBC), liver function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Prothrombin time, time and concentration, Anti-tissue transglutaminase antibodies (IgA) by ELISA (enzyme-linked immunosorbent assay) considered positive if > 10 U/ml, anti-endomysial (IgA EMA) antibodies (positive or negative) by Indirect immunofluorescence, Stool Ag for H. pylori, Immunoglobulins level, Upper gastrointestinal endoscopy with multiple biopsies for histopathological examination from the stomach (body and antrum), duodenum first and second part and jejunum, also CLO test (Campylobacter-like organism test) for diagnosis of H. pylori infection . Histologically, Giemsa stain was used for diagnosis of H. pylori while the presence of intraepithelial lymphocytosis (IEL) and villous atrophy was diagnostic of CD in addition to blood markers. The participants were classified into two groups (positive and negative H. pylori infection) according to the histopathological diagnosis of H. pylori infection. HLA DQ 2/8 by PCR SSO (sequence-specific oligosaccharides) was done for specific cases (with negative TTG and endomysial Ab with histopathology diagnostic of CD).

Campylobacter-like organism test (CLO) is a rapid diagnostic test for Helicobacter pylori. Depending on the ability of H. pylori to secrete urease enzyme, catalyzes the conversion of urea to ammonia and carbon dioxide. Patients should discontinue antibiotics and bismuth three weeks before the test. These agents may suppress the presence of H. pylori making it difficult to detect. Patients should not receive proton pump inhibitors (PPI) two weeks before as they can inhibit the growth of H. pylori.

Ethical Points

During the interview, the respondent and the children were simply informed about the aims of this study and the fact that it is done to improve the health status and education of all populations. Written consent was taken from the respondent who accompanied the child. The study followed the ethical standards of Al Qassimi Women and Children Hospital-Sharjah- MOHAP - UAE.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using numbers and percentages. The Kolmogorov- Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. The significance of the obtained results was judged at the 5% level.

The used tests were:

Chi-square test: For categorical variables, to compare different groups
Mann-Whitney test: For abnormally distributed quantitative variables, to compare two studied groups

Results

There were 50 children diagnosed with Celiac disease enrolled in the study, investigations were done and revealed 6 patients (12%) had H. pylori infection while the remaining 43 patients (86%) were negative for H. pylori infection at the time of CD diagnosis.

The mean age of the enrolled children was 7.4 ± 5.6. *(Table 1)* A total of 33 (66%) were female children. *(Table 2)*

Anti-TTG Ig A was positive in 49 patients, while one patient showed a negative result, positive Anti-TTG Ig A considered if > 10 U/mL. Endomysial AB came positive in 49 patients. Positive infection with H. pylori was detected only in 6 patients depending on the gold standard histopathology, also direct detection in stool and CLO test were used. All cases diagnosed as H. pylori infection by gold standard histopathological examination, came positive with CLO test and direct detection of stool Ag.

In the current study, only one patient was diagnosed with Seronegative celiac disease (SNCD), with the negativity of blood markers for Celiac disease including anti-TTG Ig A, Endomysial Ab, and anti-gliadin. This patient had normal Ig A was 115.0 mg/dL (N 34-305), HLA DQ 2/8 positive for Celiac disease by PCR SSO (sequence-specific oligosaccharides) intermediate resolution. He was negative for H. pylori infection. His histopathology showed patchy loss of villiform architecture with flattened to atrophic villi, dense lympho-plasma cells infiltration, patchy intraepithelial lymphocyte infiltrates (25-30/100 enterocytes), eosinophils (10-15/HPF). Immunohistochemical stains (DAKO kit), Mucosal lymphocytes are Strongly positive for CD.

Gastritis was found in 12 patients (27.9%) in the negative H. pylori group and found in all patients (100%) of the H. pylori-positive group. With the inflammation involved lamina propria characterized by numerous H.pylori are seen in Gemisa stain in the group positive for H. pylori.

Table 1: Gender distribution among the studied groups

Sex	**H. pylori Negative group** ***n*** **= 44**	**H. pylori Positive Group** ***n*** **= 6**	***P*-value**

	N	**%**	***n***	**%**	
Male	15	(34.88)	2	(33.33)	0.177
Female	28	(65.12)	4	(66.67)	

Table 2: Age of the studied groups

Studied variables	**H. pylori Negative group *n* = 44**	**H. pylori Positive group *N* = 6**	***P*-value**
mean of age (years)	7.5 ± 5.3	7.3 ± 5.9	0.086

Table 3: Anti TTG IgA among the studied groups

Parameters	**H pylori Negative group *N* = 44**	**H. pylori Positive Group *N* = 6**	***P*-value**
TTG IU/ml	**135.9 ± 48.5**	**136.5± 50.52**	**0.75**

Table 4: Endomysial Ab among the studied groups

Endomysial Ab	**H. pylori Negative group *n* = 44**		**H. pylori Positive Group *n* = 6**		***P*-value**
	N	**%**	***n***	**%**	
Positive	42	(97.7)	7	(100)	0.177
Negative	1	(2.3)	0	(0)	

Table 5: Histopathology of the studied groups among the studied groups

Histopathology	**H. pylori Negative group *n* = 44**		**H. pylori Positive Group *n* = 6**		***P*-value**
	N	**%**	***n***	**%**	
Intraepithelial lymphocytosis (IEL)	44	(100%)	6	(100%)	0.50
Villous atrophy	44	(100%	6	(100%)	

Table 6: Comparison between the H. pylori-infected and non-H. pylori-infected groups regarding hemoglobin, ferritin, and F. Calprotectin

Parameters	**H pylori Negative group *N* = 44**	**H. pylori Positive Group *N* = 6**	***P*-value**
Hemoglobin g|dL	**10.9 ± 2.51**	**10.5± 2.42**	**0.85**
Ferritin ng|mL	**24 ± 18**	**25 ± 16**	
F. Calprotectin µg/g of feces	**340 ± 116**	**360 ± 150**	

Discussion

Infection can trigger autoimmune disease, the mechanisms include molecular mimicry, epitope spreading, formation of immune complex, high levels of pro-inflammatory cytokines such as interferon (IFN)-γ, and Imbalance of T regulatory/Th17.

In this study, female children diagnosed with CD were more common than male children, this finding runs in harmony with other studies which documented increased prevalence of CD amongst females with a male: female ratio of 1:2.8 *(5)* The difference in gender and age did not show a statistically significant difference between H. pylori and non-H. pylori-infected groups. (*Table 1) and* (*Table 2)*

This study did not show any statistically significant difference between the H. pylori-positive and H. pylori-negative groups regarding histopathological findings, Anti-tissue transglutaminase antibodies, and anti-endomysial (IgA EMA) antibodies. This is the difference from other studies that reported the increased prevalence of H. pylori infection in patients with celiac disease. (6) this can be explained by the concept of they are studied by different age groups or not studied at the time of CD diagnosis.

Serological markers for celiac disease were positive in 49 patients (98%), and only one patient was diagnosed with the Celiac disease with negative serological markers of Anti-tissue transglutaminase antibodies and anti-endomysial (IgA EMA) antibodies, this patient had normal IgA level, Anti-tissue transglutaminase antibodies had Sensitivity up to 97%, and specificity around 96%. The IgA EMA represents the most specific test, approximately 100%, with a 94% sensitivity and 97% diagnostic accuracy. *(7)* Other studies showed positive EMA in 77% of atrophic villus patients and only in 33% of non- atrophic villus patients. While IgA anti-tTG was positive in all the patients with villus atrophy and absent in those with partial villus atrophy. This difference may be because our patients were selected at the time of diagnosis. *(8)*

The current study did not show any statistically significant difference between the 2 groups (H. pylori-infected children and non-infected group) regarding Anti-tissue transglutaminase antibodies (IgA) and anti-endomysial (IgA EMA). (Table 3) and (table 4), also there is no histopathological difference between the 2 groups. (table 5)

No-biopsy approach for diagnosis of coeliac disease is helpful in children with high serum IgA class antibody against transglutaminase ≥ 10 times the upper limit of normal values with positive endomysial antibodies (EMA-IgA) in a second serum sample. Children with positive TTG IgA < 10 times the upper limit of normal value should undergo biopsies to decrease the risk of a false positive diagnosis. Human leukocyte antigen (HLA) testing and the presence of symptoms are not required for a serology-based diagnosis without biopsies. *(9)*

The human leukocyte antigen (HLA) is one of the main factors involved in the pathogenesis of the celiac disease. More than 90% of affected children express HLA-DQ2 molecules; the others express HLA-DQ8. When T-lymphocytes in the intestinal mucosa espoused to gluten peptides, they will proliferate with cytokine production. *(10)*

This study did find a statistically significant difference between both groups regarding hemoglobin level, ferritin level, and fecal calprotectin. (Table 6)

The association between H. pylori and CD is conflicting. Different studies showed different results as Helicobacter pylori can trigger *(11)*, doesn't affect *(12)*, or protects against CD *(13)*, this study did not find a correlation between H. pylori infection and CD in children at the time of CD diagnosis. H. pylori infection and CD have different histopathological features.

Conclusion

This study did not find a correlation between H. pylori infection and CD at the time of CD diagnosis. However, further studies are needed to assess if H. pylori have a potential role in the pathogenesis of CD.

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