

***Helicobacter pylori* Infection as a Risk Factor in Patients Suffering from Food Allergy and Urticaria**

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H. pylori infection is common worldwide. Many intestinal and extra intestinal manifestations have been associated with *H. pylori* infection. *H. pylori* destruct the gastric lining which allows food allergens to get access to blood, predisposing to Food allergy. Previous works considered chronic urticaria as a known symptom for food allergy and a skin manifestation for *H. pylori* infection. The aim of this work is to provide evidence based recommendation for detecting *H. pylori* antigen in stool in patient suffering from both food allergy and chronic urticaria. We determined the frequency of *H. pylori* Ag in stool in a group of patients complaining from both disorders and compared it with a group of apparently healthy control subjects with no history of either urticaria or food allergy. Our results showed that the frequency of *H. pylori* Ag in stool in control group was 62.5 %, while, it was 97 % in patient group. When we calculated the risk of *H. pylori* infection in predisposing to both disorders, odds ratio was 18.6. According to these results we concluded that *H. pylori* is a risk factor for developing chronic urticaria and food allergy and we recommend testing for *H. pylori* Ag in stool in patients complaining from these disorders.

H*elicobacter pylori* (*H. Pylori*) is the most common human pathogen worldwide, infecting an estimated 50 % of the global population (Malfertheiner *et al.*, 2012, Mogaddam *et al.*, 2015). The bacterium, unless treated, cause peptic ulcer, lifelong gastritis causing abnormal epithelial growth, gastric atrophy and intestinal metaplasia. Eventually the infection ends with mucosa-associated lymphoid tissue lymphoma and gastric cancer (Yong *et al.*, 2015, Sugano *et al.*, 2015, Gu *et al.*, 2015).

The key patho-physiological event occurs during *H. pylori* infection depends on the initiation and continuation of chronic infection activities. *H. pylori* infection results in gastric mucosal infiltration by neutrophils and monocytes. *H. pylori* also secrete enzymes like urease, catalase, lipase and phospholipase which play an important role in gastric inflammation. Some authors suggested that increased vascular permeability increases the exposure to food allergens which result in food allergy to different food allergens (Magen & Delgado, 2014).

Number of skin diseases like chronic urticaria, rosacea, psoriasis, Sjögren syndrome, Henoch-Schönlein purpura, alopecia areata, Sweet disease, systemic sclerosis, atopic dermatitis, Behçet's disease, generalized pruritus (itch), nodular prurigo, immune thrombocytopenic purpura, lichen planus, and aphthous ulceratio have also been correlated with *H. pylori* (Wedi & Kapp, 2002, Hernando-Harder *et al.*, 2009).

Many Previous studies tried to find the association between *H. pylori* and chronic urticaria, from one hand and the relation of *H. pylori* and food allergy from the other hand. However, there is no conclusion that *H. pylori* is associated with any. As a result, detection of *H. pylori* infection is not yet, a recommended routine investigation for patients suffering from urticaria and food allergy. The aim of this study is to detect whether *H. pylori* infections is a risk factor to develop urticaria and food allergy and whether it is recommend to routinely detect *H. pylori* Ag in stool in patient with urticaria and food allergy.

Subjects and Methods

Patients included in the study were attending either Allergy and Immunology Unit or dermatology outpatient clinic, Faculty of Medicine, Zagazig University between July 2014 and July 2015. All patients gave consent to participate in the study.

Study design

The study was done in two stages, the first stage was a case/ control study and the second stage was a cohort study for those proved to suffer from *H. pylori* infection.

Patient group

Out of 247 patients suffering from urticaria, the study included 64 patients who fulfilled the inclusion criteria.

Inclusion criteria

Inclusion criteria include Adult Patients above or 18 years old, suffering from chronic urticaria at least 6

weeks and have food allergy as diagnosed by history, measuring specific IgE in blood, skin prick test and oral provocation test.

Exclusion criteria

Criteria for exclusion included: Children, Coexistence of serious concomitant illness (e.g. decompensated liver cirrhosis or uremia), pregnant and nursing women, Coexistence of dermatological diseases other than chronic urticaria and failure to get consent.

Control group

64 Healthy people with no history of allergic diseases, or chronic diseases.

Laboratory work for all cases and control include CBC, Urine analysis, stool analysis and detection of *H. pylori* infection Ag in stool.

Table 1. Subjects included in the study

	Case	Control
Number	64	64
Age range/median	18-60/39	18-62/42
Female/male	39/25	36/28
Duration of urticaria (rang/median)	6-240/ 160 weeks	No history of urticaria

Diagnosis of *H. pylori* infection

H. pylori infection was diagnosed by detecting Ag in stool using ELISA kit (International Immuno-Diagnostics MICROWELL) according to manufactures guidelines. Briefly, to each antibody coated well, one of five calibrators or an aliquot of diluted stool sample was added, and if *H. pylori* Ag is present, it would bind to the antibody. All unbound material is then washed. Enzyme conjugate was then added, followed by TMB chromogenic substances. The reaction was stopped by adding stop solution and the intensity of color is proportionate to the concentration of antigen. Optical density was measured using microwell ELISA reader at 450nm and concentration of Ag was then calculated. A sample was considered negative if concentration of *H. pylori* Ag in stool was below 15ng/ml and positive if the concentration was above 20ng/ml.

Patients who were positive, were treated according to the following regimen therapy with omeprazole (20 mg twice daily), amoxicillin (1 g twice daily), bismuth subcitrate (240 mg twice daily), and clarithromycin

(500 mg twice daily) for 2 weeks (Chey & Wong 2007). The patient was retested for *H. pylori* Ag in stool 6 weeks after the end of treatment to ensure efficacy of treatment. To detect the efficacy of eradication treatment on urticarial symptoms, cases were assessed 3 months after treatment, using a three-point rating scale, that is, complete remission, partial remission (50% or more), or no improvement.

The severity of urticaria was scored according to Urticaria activity score (UAS). The UAS consisted of the sum of the wheal number score and the itch severity score (Bhor & Pande, 2006) 0 = No symptoms, 1=Less than 6 small wheals and mild itching, 2= 6-12 wheals and moderate itching, 3= 3 - > 12 wheals is covered and severe itching.

The diagnosis of food allergy

History: Repeated clinical manifestations related to ingestion of certain food is highly suggestive of food allergy.

Detection of food specific IgE against using Allergy Screen Immunoblot for analysis of specific IgE in human Serum (MEDIWISS, Germany). Patient's serum is allowed to react with special allergens bound to the surface of nitrocellulose membrane lying in a reaction trough. Anti IgE coupled with biotin is then added. Finally streptavidine is added which conjugate with alkaline phosphatase. Color reaction develops in the form of precipitates on the test strip. Color is directly proportional to the amount of specific IgE in the serum.

Evaluation is carried out after complete drying of the strip with CCD camera (improve C, Rapid Reader).

The reaction trough contains the following allergen: Almond, Apple, Peanut, Banana, Cocoa, Casein, Strawberry, Chicken meat, Citrus mix, Cod fish, Crab, Egg white, Egg yolk, Hazelnut, Milk, Shrimp, Wheat flour (Egy3 panel). Interpretation of the results was done according to the manufacture's guidelines as follows (Table 2).

Table 2. Interpretation of the results was done according to the manufacture's guidelines as follows:

iu/ml	Class	Allergen- specific IgE content
<0.35 iu/ml	0	None or hardly found
0.35-0.69 iu/ml	1	Low
0.7-3.4 iu/ml	2	Increased
3.5-17.4 iu/ml	3	Significantly increased
17.5-49.9 iu/ml	4	High
50-100 iu/ml	5	Very high
>100 iu/ml	6	Extremely high

Oral provocation test (OPT) to diagnose Tomato hypersensitivity

At the beginning, the patient was advised to eliminate the suspected food from his/her diet for two weeks. OPT spanned two days, the patient was given three doses of suspected food with increasing concentrations with 12 hours interval. The patient consumed the second dose if only the first dose did not give any reaction and the same with the third dose. The patient continued to record the reaction for 48 hours after the last dose. The skin was scored by the SCORAD system before the elimination diet, during the elimination diet and before OPT and then 24 and 48 hours after OET. Positive results were considered when any of the following clinical reactions were noted: urticaria, angioedema, vomiting, wheezing, abdominal pain, diarrhea, oral allergic syndrome, pruritus, erythema, rashes or worsening of atopic eczema. Early reactions were defined as clinical symptoms within 2 hours after the ingestion of the dose in OPT and late symptoms if

occurring after more than 2 hours (Čelakovská *et al.*, 2015).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (version 17.0; SPSS, Chicago, IL, USA). Data were expressed as number and percentage. Odds ratio was used to calculate the risk.

Results

H. pylori infection was diagnosed in 62 (97%) of patients while its frequency in the control group was 40 (62.5%). When *H. pylori* risk of causing urticaria and food allergy was calculated; the OR was 18.6 ($P= 0.0001$) (Table 3).

Table 3. Frequency of *H. pylori* Ag in stool in patients and controls and calculated risk of causing urticaria and food allergy

	Cases*	Control	Odds ratio
Frequency of <i>H. pylori</i> Ag in stool	62 (97%)	40 (62.5%)	18.6**

*Cases: are patients with chronic and food allergy

**At 95% confidence interval (upper and lower limits of confidence were 4.1657 to 83.0503 respectively) and $P < 0.05$ is significant.

Of the patient group 54 (84%) were found to have GIT symptoms, while 15 (23%) of the control group were found to have GIT symptoms. The chi-square statistic is 25.098. This result is significant at $P < 0.05$

When we scored the severity of urticaria according to the Urticaria Activity Scale, we found that none of cases were scored under 0 or 1 categories. 6 patient had a score of 2, 48 patient were scored as 3 and 10 suffered from urticarial wheals that almost cover the whole body (score 4) (Figure 1).

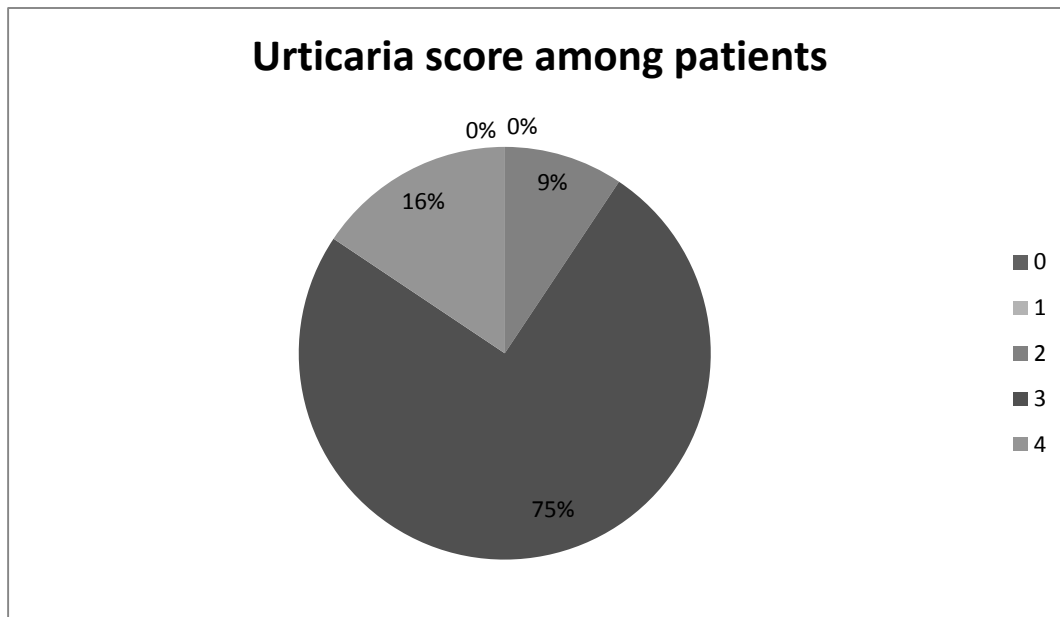


Figure 1. Scoring of Urticaria among patients with chronic urticaria and food allergy.

Diet elimination and Oral provocation test for tomato diagnosed 46 (72%) cases as having tomato hypersensitivity reactions. The cutoff value of specific IgE for food allergy diagnosed by measuring sIgE in blood was

0.34 iu/ml. None of the control group showed significant level of any specific IgE. The result of specific IgE and oral provocation tests are shown in Figure 2.

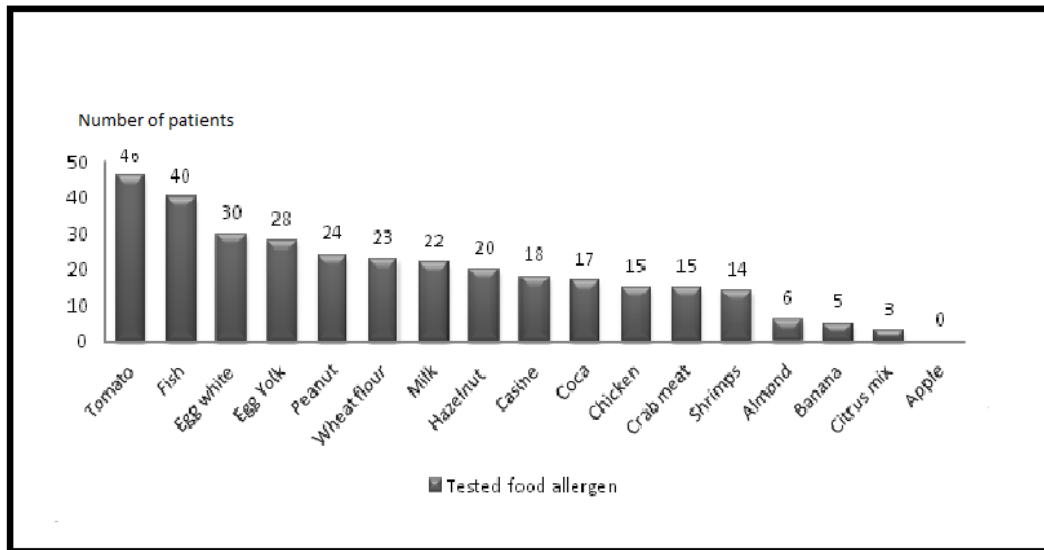


Figure 2. Frequency of different food allergen among patients with chronic urticaria and food allergy.

When we followed patients after treatment with eradicating therapy for three months to detect the effect of anti-helicobacter treatment on symptoms remission, we found that none of the Patients showed complete remission of urticaria or symptoms associated with food

allergy like angioedema, wheezing, abdominal pain, diarrhea, oral allergic syndrome, pruritus, erythema, rashes or worsening of atopic eczema while 48 (75%) showed partial remission and 16 (25%) experienced complete (Figure 3).

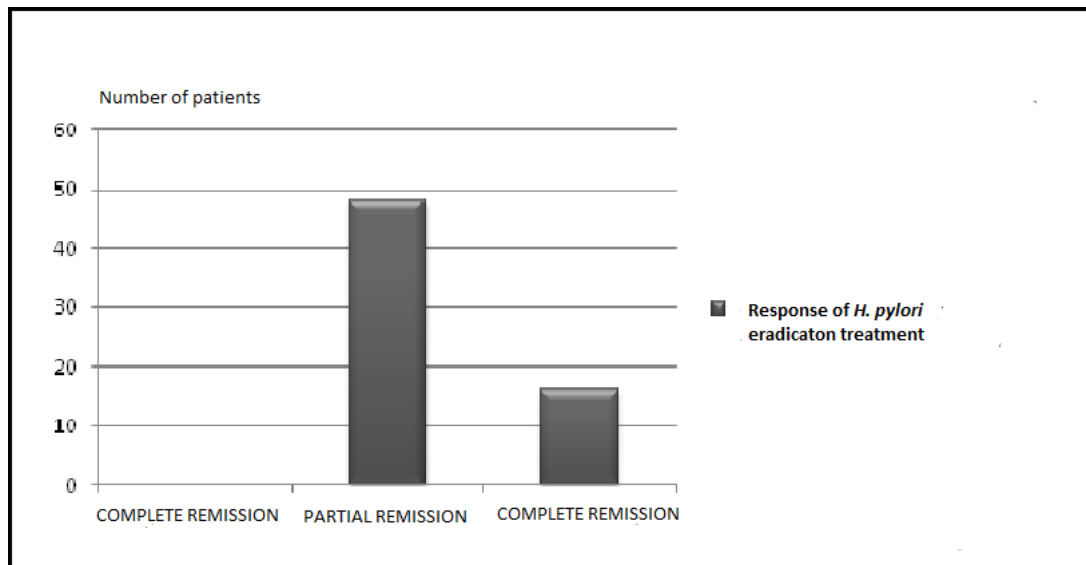


Figure 3. Effect of eradication of *H. pylori* on signs and symptoms of urticaria and food

Discussion

Stomach plays an important role in the protection against allergic conditions. Being a double layered barrier (continuous epithelium and thick lining mucus layer), it prevents various molecules (bacterial, viral, food and others) from passing across (Matysiak-Budnik & Heyman, 2002).

H. pylori destructs the gastric barrier and this allows various food allergens to pass across the injured gastric wall. IgE developed in response to this exposure and food allergy is thus a disease that may complicate *H. pylori* infection (Matysiak-Budnik *et al.*, 2003, Magen & Delgado, 2014). Urticaria is also another complication of *H. pylori* infection, in the same time urticaria is a major manifestation of food allergy (Kutlubay *et al.*, 2014, Gu *et al.*, 2015).

The aim of this study was to determine whether detection of *H. pylori* antigen in stool in patient suffering from urticaria and food allergy is recommended to be one of the basic investigations or not, and also to determine the effect of treatment of *H. pylori* on symptoms remission.

According to our results 62.5% of control group were having *H. pylori* Ag in stool, This high incidence is expected , as it is estimated that *H. pylori* infects more than 50% of the world population, the prevalence may even increases in the developing countries (Malfertheiner *et al.*, 2012, Chiu *et al.*, 2013). Meanwhile, it was detected in 97% of the case. There is thus about 20 fold (OR 18.6) increase in the risk of developing food allergy and urticaria in patient harboring the bacilli in their gastrointestinal tract (Table 3). While, some studies have reported an association between *H. pylori* infection and food allergy (Matysiak-Budnik *et al.*, 1998), other studies however, could not establish this relationship and *H. pylori* infection was insignificant risk

factor in predisposing for food allergy or urticaria (OR 1.0) (Kolho *et al.*, 2005, Baccioglu *et al.*, 2008).

Food allergy (FA) is a serious disease that significantly affects the quality of life of patient and their families (DunnGalvin *et al.*, 2015). It is a growing problem worldwide, especially in developing countries. It is estimated that food allergy affects 1% to 2% but less than 10% of the population (Sicherer & Sampson, 2014). Food allergy has variable symptoms with various degrees of severity, ranging from mild symptoms up to anaphylactic shock. FA most commonly affects the skin (atopic dermatitis, urticaria, angioedema, eczema and various skin rashes) Frequently, gastrointestinal manifestations like Dyspepsia, colic, diarrhoea, vomiting, gastroesophageal reflux, malabsorption syndromes are associated with cutaneous (Boyce *et al.*, 2011, Macchia *et al.*, 2015)

In this study all patient were selected to suffer from urticaria, statistically significant portion of cases who had the infection 84% had reported to have GIT symptoms while, only 23% of the control who had *H. pylori* infection had GIT symptom $P < 0.05$. We must here note that both helicobacter infection and food allergy cause GIT symptoms and thus determining the exact cause of GIT symptoms was difficult. Also, we have to note that the severity of GIT symptoms associated with *H. pylori* infection is associated with the bacterial virulence factors. As an example, presence of Cag A gene has been found to cause more intense infiltration to gastric mucosa and more injury Wedi *et al.*, 1998, Corrado *et al.*, 1998, Abdou *et al.*, 2009). Study of *H. pylori* virulence factors and the association of various strains with different intestinal and extra intestinal manifestation must be taken in attention.

H. pylori increases the absorption of intact food antigen across the corpus gastric mucosa.

This phenomenon may contribute to the maintenance of gastric inflammation and could play a role in the development of allergic sensitization to dietary antigens in susceptible individuals (Matysiak-Budnik *et al.*, 2004)

In this study, diagnosis of Tomato hypersensitivity was done according to diet elimination and oral provocation test, because it was not listed in the panel of sIgE used in the study. According to our results, Tomato antigen is the major cause of food allergy in Egyptian population studied 23 (72%), This result is aided by another study done on Spanish Mediterranean population, who found that allergy to tomato is one of the most prevalent vegetable allergies (Larramendi *et al.*, 2008, López-Matas *et al.*, 2015, Mascheri *et al.*, 2015). The second common cause was fish then Egg white, Egg yolk, followed by peanut, Wheat flour, Milk and Hazelnut. It is widely accepted that the major 6 types of foods commonly associated with food allergies are (milk, wheat, egg, soy, tree nuts/peanuts, and fish/shellfish (Kliwer *et al.*, 2015, Szépfalusi *et al.*, 2015, Patel & Volcheck, 2015)

Many studies have proved the relationship between *H. pylori* and chronic urticaria (Wedi & Kapp 2002, Kaplan & Greaves, 2009), urticaria is also a major symptom of food allergy. Both factors, could thus explain the fact that all cases included in this study were suffering from moderate to severe urticaria. Only 6 patients had score 2, while, 48 patients experienced urticaria score 2 and 10 patients had a score of 3, None of patients had score 1. The fact that *H. pylori* infection is associated with more severe forms of urticaria was supported by (Abdou *et al.*, 2009, Persechino *et al.*, 2012).

75% of the *H. pylori*-positive urticaria group experienced incomplete remission after receiving eradication therapy for *H. pylori*, and 25% did not feel with any difference in

symptoms at all. For explaining this we must take in our accounts that two eliminates are predisposing for urticaria in this group of patients. 1) Food allergy associated with *H. pylori* infection, and in this case, once the body has been sensitized by food allergen, the process of urticaria is more related to the presence or absence of food allergens than the presence or absence of *H. pylori*. 2) *H. pylori* infection itself can cause chronic urticaria. Other studies have shown that good proportion of patient with urticaria associated with *H. pylori* infection showed complete remission after treatment when it is not associated with allergic element (Magen *et al.*, 2007, Chiu *et al.*, 2013).

Finally, we conclude that *H. pylori* is a risk factor for developing food allergy and urticaria and so, we recommend adding the fecal *H. pylori* Ag detection in the work up of patients suffering from urticaria and food allergy. We also recommend having further researches regarding the relationship between *H. pylori* infection, the bacterial virulence factors, and *H. pylori* associated extra-intestinal manifestations.

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