The presence of H.pylori in cases of chronic idiopathic urticaria

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Abstract

Introduction: Urticaria (or hives) are a kind of skin rash notable for dark red, raised, itchy bumps. Chronic urticaria, defined as urticaria that persists for longer than 6 weeks, it is not a single disease but a reaction pattern that represents cutaneous mast cell degranulation, resulting in extravasation of plasma into the dermis and the patients may not improve or may depend on medication for years to relieve symptoms. chronic urticaria is one of the most common problems facing dermatologists and other specialities. It is the problem which bothers both the patient and the dermatologist. Traditionally, the approach in patients with chronic urticaria (when physical etiology has been excluded) has been to order a panel of laboratory tests to discover an occult medical condition responsible for the skin findings. In many patients, an extensive workup does not discover an etiology. Patients in whom no explanation for his urticaria are said to have chronic idiopathic urticaria. Various infectious agents have been reported as causes of urticaria, including Helicobacter pylori, which is a common worldwide bacterial infection. Its role in inducing allergic conditions, such as chronic urticaria, has been suggested in some reports and ignored in others.

Aim: In our research, we want to look for the prevalence of Helicobacter pylori in the serum of patient who presented with chronic urticaria .The patient has endure treatment and is not cured besides partial treatment causes temporary relive of symptoms. So, it is important to make the right decisions regarding the treatment of chronic urticaria by adding triple therapy for those who are H.pylori positive.

Subjects and Methods: This study is a non controlled , consecutive interventional study involving 60 patients during the period from November 2012 to April 2013 with history of urticarial lesions of > 6 weeks, to search for the possible cause of their chronic urticaria.

Results: Among 60 patients suffering from chronic Urticaria only 40 (66.7%) patients were enrolled in the study with chronic idiopathic urticaria.

25 patients (62.5%) of chronic idiopathic urticaria were infected with H.pylori and 15 patients (37.5%) had negative serology for H.pylori . 80% of patients with positive H.pylori had G.I.T symptoms ,18 patients (72%) were achieved eradication with the first line therapy while 5 patients (20%) required the second line therapy for eradication. In 2 patients (8%) H.pylori persisted despite two courses of eradication therapy. Response to eradication therapy was evident in 19 patients (76%) in whom H.pylori was eradicated while 4 patients (16%) showed no response despite eradication of H.pylori . Two patients (8%) with persistent H.pylori infection showed no improvement in the urticarial symptoms at the end of study period.

Conclusion: The results of our study strongly suggest that H.pylori should be specifically tested in all patients of CIU, to identify subset of patients who are infected and who could benefit from eradication therapy. H.pylori should be included in the diagnostic work up of all patients with CIU.

Key words: H.pylori, chronic idiopathic urticaria , chronic urticaria

Aim of the Study

The aim of this study is to identify cases who presented with chronic urticaria at the health center; to detect the appearance of *H. pylori* in the serum of patients with chronic idiopathic urticaria.

Justifications of the Study

Chronic urticaria is one of the most common problems which we face in our clinical practice. It is the problem which bothers both the patient and the dermatologist. Traditionally, the approach in patients with chronic urticaria (when physical etiology has been excluded) has been to order a panel of laboratory tests to uncover an occult medical condition responsible for the skin findings. In many patients, an extensive workup does not uncover an etiology. Urticaria rarely is the sole manifestation of an underlying medical problem. Patients in whom no explanation for the urticaria is established are said to have chronic idiopathic urticaria. Various infectious agents have been reported as causes of urticaria, including Helicobacter pylori, which is a common worldwide bacterial infection. Its role in inducing allergic conditions, such as chronic urticaria, has been suggested in some reports and ignored in others.

In our research, we want to look for the prevalence of Helicobacter pylori in the serum of patients who presented with chronic urticaria. The patient has endured treatment and is not cured besides partial treatment causes temporary relief of symptoms, so it is important to make the right decisions regarding the treatment of chronic urticaria by adding triple therapy for those who are *H.pylori* positive.

Literature Review

Urticaria (from the Latin urtica, nettle (whence It. ortica, Sp. ortiga, Pg. urtiga) urere, to burn) (or hives) is a kind of skin rash notable for dark red, raised, itchy bumps. [1]

Chronic urticaria, defined as urticaria that persists for longer than 6 weeks, is not a single disease but a reaction pattern that represents cutaneous mast cell degranulation, resulting in extravasation of plasma into the dermis and the patients may not improve or may depend on medication for years to relieve symptoms. [1]

The primary subgroups of chronic urticaria include physical urticaria (symptomatic dermatographism, cholinergic urticaria, pressure urticaria), urticaria secondary to an underlying medical condition, and chronic idiopathic urticaria. Physical urticaria, which is reproducible with the appropriate stimuli, can be identified with a thorough history and challenge testing. [2]

Traditionally, the approach in patients with chronic urticaria (when physical etiology has been excluded) has been to order a panel of laboratory tests to uncover an occult medical condition responsible for the skin findings. In many patients, an extensive workup does not uncover an etiology. Urticaria rarely is the sole manifestation of an underlying medical problem. Patients in whom no explanation for the urticaria is established are said to have chronic idiopathic urticaria; however, findings suggest that in 25-45% of patients, chronic idiopathic urticaria is not idiopathic but is an autoimmune disease termed chronic autoimmune urticaria.[2]

After eliminating the physical urticarias and urticarial vasculitis, chronic urticaria can be divided into autoimmune chronic urticaria (45%) and idiopathic chronic urticaria (55%).[3]

Approximately one third of patients with chronic urticaria have either or both antithyroglobulin antibody and antimicrosomal antibody, and up to one fifth have abnormal thyroid function. A positive functional anti-Fc ε R test result supports an autoimmune basis and the affected patients may be categorized as having autoimmune chronic urticaria. Approximately one third of patients with chronic urticaria may develop angioedema after administration of aspirin or other nonsteroidal anti inflammatory drugs.[4]

Approximately 85% of histamine receptors in the skin are of the H1 subtype, with the remaining 15% being H2 receptors. The combination of H2 receptor antagonists with an H1 receptor antagonist provides small additional benefit. Doxepin blocks both types of histamine receptors and is a much more potent inhibitor of H1 receptors than diphenhydramine or hydroxyzine. [5]

A number of factors have been reported to cause chronic urticaria, and these include medications (aspirin, other non-steroidal anti-inflammatory drugs, opioids, ACE inhibitors, and alcohol), contact with an inciting agent, latex (especially in health care workers), plants, animals (e.g. caterpillars, dander), food (e.g. fish, garlic, onions and tomato), arthropod assault (the most common cause of papular urticaria) and infections (HBV, HSV, Streptococcus, Mycoplasma, Helicobacter.pylori and Mycobacterium tuberculosis). [6,7]

Urticaria has been associated with a number of autoimmune diseases,.including systemic lupus erythematosus, cryoglobulinemia, juvenile rheumatoid arthritis and autoimmune thyroid disease, including Graves disease.[8,9] Urticaria is a feature of Muckle-Wells syndrome (amyloidosis, nerve deafness, and urticaria) and Schnitzler syndrome (fever, joint/bone pain, monoclonal gammopathy, and urticaria).[10]

Little evidence exists to support the concern that chronic urticaria is a cutaneous sign of occult internal malignancy. In a study of 1,155 patients with chronic urticaria in Sweden, Sigurgeirsson found no association with cancer, although acquired angioedema associated with C1 inhibitor depletion may be associated with malignancy.[11]

Physical factors are the most commonly identified etiologies of chronic urticaria, accounting for approximately 20% of cases. [14]

Chronic urticaria may be a consequence of fibromyalgia-neurogenic skin inflammation and psychological factors are reported to play a role in a number of patients. [12]

Avoidance of mental stress, overtiredness, alcohol, non-steroidal anti-inflammatory drugs, and tight-fitting garments is recommended. Nocturnal pruritus may be reduced by lukewarm bathing and keeping the ambient temperature of the bedroom cool. Application of lotions with menthol and phenol (Sarna) provide prompt relief of pruritus for some patients. [13]

Non-sedating antihistamines remain the mainstay of treatment. Many patients find pruritus less troublesome during the daytime, with pruritus maximized at night when there are fewer distractions. An additional nocturnal dose of a sedative antihistamine such as hydroxyzine or doxepin may be added to the morning dose of a low-sedation anti H1 antihistamine. Doxepin should not be used in patients with glaucoma and should be used with extreme caution in elderly patients or those with heart disease. Doubling the labeled dose of low-sedating antihistamines may benefit some patients, and increasing the dose of these antihistamines is often the safest therapeutic approach for patients who do not have an adequate response to the.conventional.dose.of.these. medications. [14]

Patients who respond poorly to antihistamine therapy or who are known to have urticaria in which the inflammatory infiltrate is neutrophil predominant may require the addition of colchicine (0.6 mg twice daily) or dapsone (50-150 mg once daily) to the treatment regimen (except patients with glucose-6-phosphate dehydrogenase [G-6-PD] deficiency). Patients with autoimmune urticaria may benefit from methotrexate or cyclosporine.[13- 15]

A possible association between *H. pylori* infection and chronic urticaria has been proposed [16-22], and several mechanisms have been implicated. One proposed mechanism is that an increase in gastric vascular permeability during infection results in greater exposure of the host to alimentary allergens [23].In support of this suggestion duodenal ulcer patients have a higher incidence of allergic manifestations than controls. IgE-containing cells in gastric and duodenal mucosa seem to be the culprits [24], although there is limited evidence for HP-specific IgE. Thus, the possibility that patients with urticaria develop specific IgE against *H. pylori* is an attractive pathogenic explanation that unfortunately has not been confirmed yet. [25,26]

The immunomodulatory role of *H. pylori* infection in CU is a subject of intensive debate. This immunomodulation is not only dependent on the virulence of *H. pylori* but also on host and environmental factors. An alternative possibility is that immunological stimulation by chronic infection may produce, through mediator release, a non-specific increase in sensitivity of the cutaneous vasculature to agents that enhance vascular permeability. Furthermore, IgG and IgA antibodies to 19-kDa H. pylori-associated lipoprotein were found to play a role in the pathogenesis of CU. [27,28]

Moreover, *H. pylori* causes pronounced complement consumption due to H. pylori specific antibodies. This contributes further to the pathogenesis of CU [29,30]. As recent studies have demonstrated, IgG auto antibodies against IgE and/or Fc ε Ri α can be found in the sera of one-third of patients with CU, and it is postulated that infection with H. pylori may induce production of pathogenetic antibodies possibly by molecular mimicry [31]. A growing body of evidence suggests that 30-50% of CU results from an autoimmune process involving functional histamine-releasing anti-Fcε RI α auto antibodies or less commonly, anti IgE auto antibodies [32,33]. Appelmelk et al first demonstrated the molecular mimicry between *H. pylori* and lipopolysaccharide (LPS) and anti-Lewis antibodies in autoimmune type-B gastritis. [31] Further evidence was provided by the highly positive autologous serum skin test (ASST) results in chronic urticaria patients with *H. pylori* IgG antibodies [34].

Diagnosis of Helicobacter pylori

The available diagnostic methods are summarized in Table 1 (top of next page). Carbon 13 or 14 urea breath test (UBT) and the stool antigen tests are non-invasive tests that can be used for testing in the clinical setting. Serology kits for the presence of antibodies in the blood can also be applied with high accuracy. The commonly used medication proton pump inhibitor leads to false negative breath and stool antigen tests, but does not affect the results of serological tests. Proton pump inhibitors should be stopped at least 2 weeks before performing a breath test or a stool antigen test. It is recommended to perform a follow-up test in patients who underwent H. pylori eradication using urea breath tests. If this diagnostic procedure is not available a laboratory-based stool antigen test, preferably using monoclonal antibodies, could be used [35].

Treatment of *H. pylori* infection with triple therapy (a proton-pump inhibitor such as omeprazole 40mg once daily, amoxicillin 1g twice daily and clarithromycin 500mg twice daily for 7 to 14 days) cures up to 90% of individuals. [36].

Subjects and Methods

Type of Sampling: Consecutive sampling involves taking every subject who presents him/herself to the hospital over a specified time period.

Study Design: This study is a non controlled interventional study.

Data collection methods: In the same period permission was granted by the ethics committee and informed consent was taken from all patients. Patients were examined individually. Each patient with Chronic urticaria had an evaluation sheet which was filled by the principal

Non-invasive tests	Carbon 13 or 14 urea breath test
	Stool antigen test
	Serology
Invasive diagnostic tests	Histology
	Rapid urease test
	Molecular methods

Table 1: Diagnostic Methods of Helicobacter pylori infection.

Evaluation sheet for Urticaria

Date: Case No. :

Name: Sex: Age:

Address: Telephone No.:

Chief Complaint:

**Present H. :*

-Duration:

-Distribution:

-Ass. With Angioedema:

-Aggravating factors:

-Relieving factors:

-GIT symptoms: nausea, vomiting, abdominal pain, heart burn

-Hx. of drugs:

-Systemic disease: HTN, DM, Liver, Renal, Vascular

**Past medical history:*

**Drug history:*

**Family history :*

**Physical Exam :*

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*Investigations :

Step 1: C.B.C, ESR, LFT, RFT, GUA, STOOL Analysis, IgE, HBV, HCV, T3, T4, TSH,ANA.

Step 2: H.pylori detection by ELISA(+ve/-ve).

****Treatment :***

Table 2 : Evaluation sheet for urticaria

	Male		Female		
	CIU	CU	CIU	CU	Total
11-20	3	2	5	5	15
21-30	1	2	10	3	16
31-40	1	1	6	2	10
41-50	1	0	8	4	13
51-60	2	0	3	1	6
Total	8	5	32	15	60

Table 3: prevalence of chronic urticaria and chronic idiopathic urticaria among different age groups.

investigator (Table 2 - opposite page) before and after therapy, and the findings were compared statistically.

Sample size : 60 human subjects.

Methods: Sixty patients attending the dermatology clinic, at King Khalid Hospital, Najran, Saudi Arabia during the period from November 2012 to April 2013 with a history of urticarial lesions of > 6 weeks as in Figures 1 and 2, were screened to elicit the possible factors of their chronic urticaria. The preliminary screening panel for each patient included complete history, physical examination and the following laboratory tests: complete blood count including differential count, total eosinophil count, sedimentation rate, urine analysis, liver function test, serum test for hepatitis B and C, T3 (free), T4 (free), TSH, anti thyroid antibodies, stool examination for parasites and ova and total IgE (chemiluminescence). Each patient who presented with chronic Urticaria was provided with an evaluation sheet for follow up (Table 2).

Other tests which were done when indicated by patients history included: prick test with a panel of common inhalants and food allergens (animal dander, pollens, house dust mites, milk, egg, nut, tomato, wheat, peach, banana), investigation for focus of infection in various locations (teeth, upper respiratory and urogenital tract). Patients with an identifiable cause were treated accordingly and patients with Chronic Idiopathic Urticaria (chronic urticaria with no identifiable cause) were enrolled in the study (Table 2).

Inclusion criteria: All patients of Chronic Idiopathic Urticaria willing to be enrolled for the study.

Exclusion criteria: patients suffering from physical urticaria, patients less than 11 or greater than 60 years of age, pregnant females, patients who had taken proton pump inhibitors /antibiotics within the preceding 4 weeks, and presence of other concomitant serious medical and surgical diseases. Forty (8 males, 32 females) patients of CIU (66.7%) with mean age 35.5 years (11-60 years) were enrolled in this study (Table 3). Blood sampling was taken from the target population who complained of chronic idiopathic urticaria to detect H. pylori IgG and or IgA. Patients with positive HP in the blood sample were given first-line therapy comprising omeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, twice daily for 14 days.

H. pylori eradication was assessed by Urea Breath test (which has a sensitivity and specificity of 95%). [42] If H. pylori persisted after first line therapy, patients were offered second line therapy, comprising omeprazole 20 mg, amoxicillin 1000 mg, metronidazole 500 mg, twice a day for another 7 days. After completion of therapy, all infected patients were prescribed antihistamines to be used as 'rescue medicine'. Non infected patients were treated with antihistamines or steroids. All patients were followed up during the study duration of six months. Also each patient's objective response to treatment was judged using 3 variables based on the need for 'rescue medicine': complete remission (CR - no need for antihistamines), partial remission (PR - occasional need for antihistamines), and no remission (NR -frequent/daily need for antihistamines),(Table.4 - next page).

The total number of cases with chronic urticaria (CU) was 60 patients.

40 patients with Chronic Idiopathic Urticaria (CIU)

25 patients with (CIU) are (+Ve H.pylori) M:F ratio 5:20

15 patients with (CIU) are (-Ve H.pylori) M:F ratio 3:12

20 patients with (CU) M:F 5:15

H. pylori response	Number of subjects (n=25)	Objective response to treatment			
		CR	PR	CR+PR	NR
+Ve H.pylori eradicated by 1st. line therapy	18	9	7	16	2
+Ve H.pylori eradicated by 2nd. Line therapy	5	1	2	3	2
Persistent infection	2	0	0	0	2

Table 4: Objective response to treatment.
CR (complete remission), PR (partial remission), CR+PR (response to treatment), NR (no remission).

AGE By (years)	Gender			
	Male		Female	
	GIT symptoms	No GIT symptoms	GIT symptoms	No GIT symptoms
11-20	1	0	2	0
21-30	1	0	4	2
31-40	1	0	4	0
41-50	0	1	4	1
51-60	0	1	3	0
Total	3	2	17	3

Table 5: prevalence of H. pylori +Ve patient and G.I.T symptoms among different age groups.

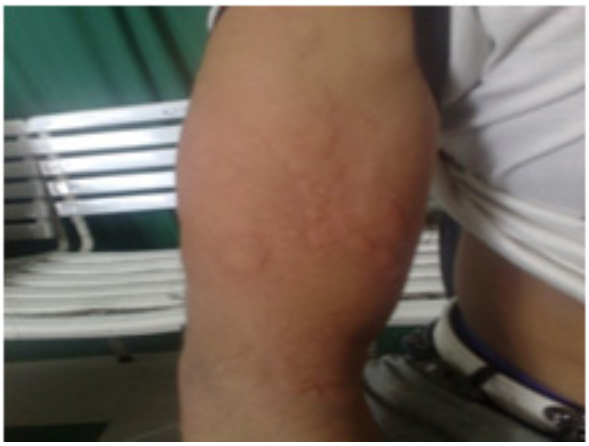

Figure 1: Urticarial lesions on the right side of the upper limb of a 20 year old male patient

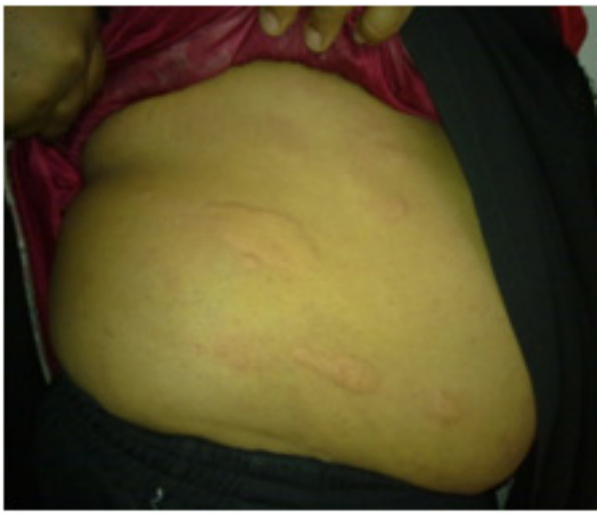

Figure 2: Urticarial lesions on the abdomen of a 42 year old female patient.

Results

Among 60 patients suffering from chronic Urticaria, male to female ratio was 13:47. 40 (66.7%) patients were enrolled in the study with chronic idiopathic urticaria. 25 (62.5%) patients of chronic idiopathic urticaria were infected with H.pylori and 15 (37.5%) patients had negative serology for H.pylori . 80% of patients with positive H.pylori presented with G.I.T symptoms and 20% without G.I.T symptoms (Table 5). 18 (72%) infected patients achieved eradication with first line therapy while 5 (20%) patients required second line therapy for eradication. In 2 (8%) patients HP persisted despite two courses of eradication therapy. Response to eradication therapy (CR + PR) was evident in 19 (76%) patients in whom HP was eradicated while 4 (16%) patients showed no response despite eradication of HP. Two (8%) patients with persistent HP infection showed no objective improvement in urticarial symptoms at the end of study period (Table 4).

Discussion

The present study was performed to assess the possible association of HP with CIU. This study is important because there is high prevalence of HP infection among the population and there are conflicting reports of association between HP infection and CIU from several western studies. In this study there is high prevalence of HP infection, with 25 (62.5%) of the patients with CIU. The high prevalence of HP infection has been previously reported in other studies, as well.[37] In the infected patients there is resolution of urticarial symptoms when HP eradication therapy was given. This is in concordance with previous studies, which have shown resolution of urticaria after HP eradication therapy. [38,39] However the role of HP as an eliciting factor for CIU is still controversial. While several authors have suggested a possible role of HP in the pathogenesis of CIU, others have shown no correlation between treatment and remission of urticaria. [38,40] A recent study in Japanese university students showed that allergic diseases are negatively associated with HP infection, especially in men. [41] Another study showed that eradication of HP infection by triple therapy significantly and equally reduces urticarial activity score in CU patients with positive and negative autologous serum test.[42]

The discrepancy between results of these different studies may be due to the different methods used for detection and establishment of HP infection or resistance of HP to therapy or recurrences shortly after successful therapy. The pathogenic mechanism that may exist between CIU and HP infection remains unknown. HP by causing inflammation in the gastrointestinal tract might facilitate absorption of antigens or unmask existing antigens. [43] Once this occurs the production of IgE antibodies responsible for urticarial symptoms might continue even after eradication of HP. Thus HP infection may perpetuate the urticarial tendency of an infected person. [43] HP infection is frequent, but it triggers urticaria only in some infected patients, so long duration studies are needed to establish natural history of HP infection with respect to urticarial symptoms, their reinfection and retreatment. Only such studies will fulfill the Koch's postulate and only then HP could be labeled as an etiological factor for CU. [43] Already there are reports of patient of CU who had gone into remission after elimination of HP and had a relapse with reinfection, which again cleared after elimination. [43] Addition of HP in diagnostic workup of patients with CIU identifies patients who could benefit from eradication therapy and thus extends the treatment options. [44]

Conclusion

The results of our study strongly suggest that HP should be specifically tested in all patients of CIU, to identify a subset of patients who are infected and who could benefit from eradication therapy. HP should be included in the diagnostic work up of all patients with CIU.

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