Role of *Helicobacter pylori* in chronic ordinary urticaria: a case-control and therapeutic study

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ABSTRACT

Background: **The term 'urticaria' is used to describe a disease that may present with wheals, angioedema or both. It is considered chronic when the attacks last > 6 weeks. A possible association between chronic urticaria and *Helicobacter pylori* infection (*H. pylori*) was suggested by a systematic review of therapeutic studies.**

Aim of the study: **To investigate the role of *H. pylori* in patients with chronic ordinary urticaria and to evaluate the effect of *H. pylori* eradication on the clinical course of chronic urticaria.**

Patients and methods: **A prospective case- control and therapeutic study was conducted on 135 patients with chronic ordinary urticaria and 186 apparently normal matched controls. All subjects were tested for *H. pylori* stool antigen and the presence of gastrointestinal symptoms was recorded. This followed by therapeutic study on a subgroup of patients with positive stool antigen test to assess the effect of triple eradication therapy of *H. pylori* including amoxicillin 1gm twice daily, clarithromycin 500mg twice daily and omeprazole 20mg twice daily for two weeks on the course of chronic urticaria by following them for six months using three points rating scale and the need for H1 blocker antihistamine as rescue medicine.**

***Results: H. pylori* stool antigen test was positive in 164(51.1%) subjects of the studied population, where 86 (63%) of patients with chronic urticaria have positive stool antigen test versus 78 (41%) among the control group with astatically significant difference(p value < 0.001, odd ratio 2.4). It was also observed that 91 (68.4%) %) out of 133 subjects with gastrointestinal symptoms had actually positive *H. pylori* infection using stool antigen test, this suggested that gastric symptoms and *H. pylori* infection was statistically associated (P < 0.001). Only 52 patients with chronic urticaria and positive *H. pylori* stool antigen test were completed the six months follow up period. The response to eradication therapy (complete remission + partial remission) was evident in 42 (80.8%) patients, that was found to be statistically significant (p value = 0.019) by comparing them with 10(19.2%) patients with no objective response. In general, no significant adverse effect was reported.**

Conclusions

1. **There is a statistically significant association of *Helicobacter pylori* infection with chronic urticaria**
2. **Eradication of *H. pylori* is a valid therapeutic option for patients with chronic ordinary urticaria and positive stool antigen test as it induces complete and partial remission in 80.8% of the cases.**

Key word: H. pylori, urticaria, angioedema

دور بكتيريا هليكوباكتور بايلوري في مرض الشرى المزمن العادي: دراسة مقارنه علاجية

الخلفية : **استخدم مصطلح الشرى لوصف المرض الذي يظهر على سطح الجلد بشكل انتبار شروي او وذمة وعائيه، و يعتبر مرض الشرى مزمن عندما تتجاوز مدة الاعراض اكثر من ٦ اسابيع. تم طرح اقتراح عن وجود ارتباط محتمل بين مرض الشرى المزمن وعدوى بكتيريا الهليكوبكتير نتيجة مراجعه منهجيه لدراسات علاجيه سابقة للبكتريا لدى مرضى الشرى المزمن.**

الهدف من الدراسة: **يصبو البحث لتسليط الضوء على دور بكتيريا هليكوباكتور بايلوري لدى مرضى الشرى المزمن العادي من خلال تقييم مدى انتشار العدوى و تقييم تأثير معالجه بكتيريا هليكوباكتور بايلوري على الاعراض السريريه لمرض الشرى المزمن.**

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طرائق العمل: ضّمنت الدراسة ٣٢١ فردا، كان منهم ١٣٥ مريض يعانون من الشرى المزمن تم مقارنتهم مع ١٨٦ شخص لا يعانون من الشرى المزمن ،كل الاشخاص المشمولين بالبحث أجري لهم فحص عينة براز لوجود مولّد المضاد الخاص ببكتيريا هليكوباكتور بايلوري وتم تسجيل وجود او عدم وجود اعراض الجهاز الهضمي.تلى ذلك متابعة فئة معينه من المرضى المصابون بالشرى المزمن وعدوى بكتريا هليكوباكتور بايلوري معا من حيث التأثير العلاجي للدواء الثلاثي ضد البكتيريا على اعراض الشرى المزمن وتم تقييم الاستجابه بواسطة المقياس ثلاثي النقاط وحاجة المرضى لمضاد الهستامين.

النتائج: أظهرت الدراسة ان ١٦٤ (٥١.١%) شخص مصاباً ببكتيريا هليكوباكتوربايلوري ،حوالي ٨٦(٦٣.٧%) شخص منهم كانوا مصابين بالشرى المزمن ايضا. تم الاستنتاج ان بكتيريا هليكوبكتر بايلوري اكثر شيوعاً عند المرضى المصابين بالشرى المزمن بعد مقارنتهم بالأشخاص الغير مصابين بالشرى المزمن من الناحية الإحصائية ($p\ value < 0.001$, $odds\ ratio = 2.4$). تم ملاحظة ان من مجموع ١٣٣ شخص كانوا يعانون من اعراض الجهاز الهضمي من كلا المجموعتين المدروسه، حوالي ٩١(٦٨.٩ %) شخص منهم كان مصاباً بعدوى بكتيريا هليكوبكتربايلوري مع وجود علاقة احصائيه معتد بها بين اعراض الجهاز الهضمي والاصابة بعدوى الهليكوباكتوربايلوري .($p\ value < 0.001$) تم متابعة حالة ٥٢ مريض مصاب بالشرى المزمن وبكتيريا هليكوباكتوربايلوري ونتيجة لذلك تم ملاحظة ان نسبة الاشخاص الذين استجابوا للعلاج (شفاء تام+شفاء جزئي) كانت ٨٠.٨ % بعد القضاء على البكتيريا مع وجود علاقة احصائية معتد بها بعد مقارنتهم بالذين لم يستجيبوا .($p\ value = 0.019$)

الاستنتاجات: وجود علاقة ذات طبيعة إحصائية بين مرض الشرى المزمن العادي واصابة المرضى ببكتيريا هليكوباكتوربايلوري.وتم استنتاج ان القضاء على عدوى بكتيريا هليكوباكتوربايلوري ذو فائدة علاجيه لدى الاشخاص المصابين بالبكتيريا والشرى المزمن.

الكلمات المفتاحية: شرى، شرى وذمي، هليكوبكتر

INTRODUCTION

The term 'urticaria' is used to describe a disease that may present with wheals, angioedema or both. They are often occurring together by similar processes resulting from superficial and deep swellings respectively. [1] The itching that is caused by urticaria can be pricking or burning and is usually worse in the evening or nighttime. [2] Estimation of the lifetime occurrence of urticaria ranges from 1-5%.[3] It is more common in women, with female: male ratio of approximately 2:1, but the ratio varies with the different physical urticarial. [4]

Based upon recently published European guidelines, urticaria is classified in to:[5]

A. Ordinary urticaria/angioedema:

It consists of wheals/angioedema that occur randomly without local physical provocation and it includes:

1. **Acute urticaria/angioedema**: isolated attacks of urticaria last < 6 weeks.
2. **Chronic urticaria/angioedema**: attacks last > 6 weeks.

Chronic urticaria is divided into two major subgroups:

a. **Chronic autoimmune urticaria (45%).**
b. **Chronic idiopathic urticaria (55%).**

B. Physical urticaria/angioedema

C. Special types of urticaria/angioedema

A possible association between chronic urticarial and bacterial infection (e.g. *Helicobacter pylori*) was suggested by a systematic review of therapeutic studies. [6]

Helicobacter pylori (*H. pylori*) a gram-negative bacterium found on the luminal surface of the gastric epithelium that can induce chronic inflammation of the underlying mucosa. [7]. The infection is usually contracted in the first few years of life and tends to persist indefinitely unless treated. [8] *H. pylori* is mainly acquired by the fecal-oral, oral-oral or gastro-oral route. [9] It has been estimated that up to half of the world's population harbor the infection in their stomach. [8] The developing world has a higher prevalence rate of infection than the developed

world, and it has been associated with both gastrointestinal and extra-intestinal complications. The organism can survive in the acidic environment of the stomach partly owing to its remarkably high urease activity; urease converts the urea present in gastric juice to alkaline ammonia and carbon dioxide. [7] Recent evidence has demonstrated that *H. pylori* infection induces autoantibody formation because of the immunogenicity of its cell envelope (polysaccharide Lewis X and Y blood group antigens) and therefore autoantibodies are formed by molecular mimicry analogous to the role of Campylobacter jejuni in the Guillain-Barre syndrome.[8,9] In addition, *H. pylori* induces HLA-DR expression on gastric epithelium and enabling these cells to behave as antigen-presenting cells. The *H. pylori* might have an indirect role in the etiology of chronic urticaria because of the reduction of immune tolerance and the induction of autoantibody formation, including anti- FcεRI autoantibodies. [10]

Aim of study

The aim of the study was:

1. To investigate the role of *H. pylori* in the patients with chronic ordinary urticaria by assessing the prevalence of Helicobacter pylori in patients with chronic ordinary urticaria by using stool antigen test.
2. to evaluate the effect of *H. pylori* eradication on the clinical course of chronic ordinary urticaria.

PATIENTS AND METHODS

Subjects

A prospective case-control and therapeutic study conducted on a sample of patients who attended the outpatient clinic of Dermatology and Venereology in Basrah Teaching Hospital in the south of Iraq during the period between 1st of September-2015 to 1st of-November-2016, where 321 individuals was enrolled in this study. Each one informed that he or she is a part of scientific study and a written informed consent obtained from each of them.

The participants were divided into two groups:

Group 1: (The cases group) which consisted of 135 patients with chronic urticaria unresponsive to treatment was made. Their age ranged from 16-80 years (mean=40.13 ± 12.6) years. All patients were interviewed and a detailed history was taken including patient age, gender, duration of illness, drug history, any history of chronic illnesses such as diabetes mellitus, autoimmune diseases and associated gastrointestinal symptoms like nausea vomiting, dyspepsia, abdominal pain, heartburn, diarrhea, hunger in the morning and any history of gastritis or peptic ulcer. In addition, patients were asked for any evidence of any other type of infection such genitourinary tract infection, respiratory tract infection, sinusitis, tonsillitis and dental infection. Clinical examination was focused on type of skin lesion, site, and if any associated angioedema , then, all the patients were investigated in the form of complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP). Some patients required general urine examination, renal function test, fasting blood sugar, liver function test, rheumatoid factor, general stool examination, thyroid function test and auto-antibody test, complement studies, food allergy blood test, and skin biopsy to exclude any underlying associated conditions.

The main exclusion criteria for this group were:

1. Certain types of urticaria like physical, contact and papular urticarial, drug induced & urticarial vusculities.
2. Urticarial lesions which presented as a feature of other dermatoses like urticarial lesion that presented with bullous dermatoses, urticarial eruption as a drug reaction, urticarial vasculitis, parasitic infestation and those with mastocytosis.
3. Pregnant patient.

4. Patient with recent ingestion of antibiotics or proton pump inhibitor for the last one month.
5. Those with gastrointestinal tract bleeding or history of renal failure, chronic liver disease, malignant disease or on immunosuppressant agents.

Group 2: (The control group) consisted of 186 apparently healthy individuals matched cases for age and sex. They were assessed for any gastrointestinal symptoms related to *H. pylori* infection. Exclusion criteria were intake of anti *H. pylori* drugs in the previous one month.

Helicobacter pylori stool antigen test

All subjects were asked to submit fresh stool samples which were tested for evidence of *H. Pylori* infection by stool antigen positivity with immunoassay-based Rapid Strip HpSA™ according to manufacturer's instructions (from CTK Biotech, Inc.). *Helicobacter pylori* stool antigen test (HpSA) was used because it is a rapid and noninvasive method with sensitivity of (95%) and specificity (95%) and it is potentially very helpful in diagnosing active and repeated *H. pylori* infection. [11] The positivity rates of HpSA were then compared between the two groups and any correlation of positivity for *H. pylori* stool Ag with chronic urticaria or with the presence of gastric symptoms was also noted. Patients with chronic urticaria in-group 1 were further assessed regarding the presence of angioedema, the duration of urticarial symptoms.

Treatment allocation

All patients with chronic urticaria who had positive HpSA were given eradication treatment after excluding those patients that had other focus of infection by history or investigations. The eradication therapy includes a combination of omeprazole 20mg BID, clarithromycin 500mg BID and amoxicillin 1gm BID for two weeks' duration. Amoxicillin was substituted with metronidazole 500 mg twice daily in patient with history of penicillin allergy. [7, 12] In addition to the use of H1 blocker in a form of loratadine 10mg once daily. At the end of eradication treatment, we tried to stop the antihistamine drug except for patients who were showing a persistent need for antihistamine kept on the smallest possible dose as a rescue medicine. [13,14] All patients were followed up monthly during the study period of six months for the following:

A. Clearance of *H. pylori* infection by stool Ag test one month after completed the eradication course by using stool antigen test. If *H. pylori* persist after first line therapy, patients were given a second line therapy comprising omeprazole 20mg BID, amoxicillin 1gm BID and levofloxacin 500mg BID for one-week duration. [7, 15]
B. Each patient's objective response to treatment was judged for any improvement in the signs and symptoms of urticaria treatment, using a three-point rating scale[16] and the need for antihistamines as rescue medicine. [13,14] According to that, patients were classified into the following three groups:
   1. Complete remission (CR), and have no need to antihistamine.
   2. Partial remission (PR), (50% or more) and occasional need for antihistamines.
   3. No response (NR), (less than 50%) and frequent/daily or almost daily need for antihistamines.
   4. Adverse effects of the treatment were also recorded.

Statistical analysis of data was made by using statistical package for social sciences (SPSS) version 20. Chi-square test and Fisher's exact test were used to determine the association between selected risk factors. P-value less than 0.05 was considered significant.

RESULTS

Three hundred twenty one subjects were enrolled in this study, there were 135 patients in-group 1 (cases) and 186 subjects belong to

group 2 (control). Both groups were matched in view of age and gender. The age of our patients ranged from 16-80 years. The mean age in-group 1 (cases) was 40.13 ± 12.6 years and in-group 2 was 39.47+14.96 years, 89(65.9%) were females and the remaining 46(34.1) patients were males with female to male ratio 2:1. About 50%of patients with chronic urticaria belong to 21-40 years of age**,** those associated with positive HpSA was most frequently (46.5%) recorded in this age group. (Table-1).

Table 1. The positivity of HpSA according to the age in both groups.

Group	HpSA + ve Individuals No. (%)	HpSA – ve Individuals No. (%)	Total No. (%)
Positive GIT symptoms	91 (68.4)	42 (31.6)	133 100)
Negative GIT symptoms	73 (38.8)	115 (61.2)	188 (100)
Total	164 (51.1)	157 (48.9)	321(100)

Correlation of *H. Pylori* stool antigen test (HpSA) with associated gastrointestinal symptoms:

Positive HpSA value was correlated with the presence/absence of associated gastrointestinal symptoms, it was observed in 91 (68.4%) %) out of 133 subjects with gastrointestinal symptoms had actually positive *H. pylori* infection according to HpSA. On the other hand, of the 188 subjects with no history of any gastrointestinal symptoms, positive stool antigen test was demonstrated in 73 (38.8%) individuals this difference was found to be statistically significant (P < 0.001), (Table-2).

Table 2. Correlation of HpSA with presence of gastrointestinal (GIT) symptoms

Age group	Hpsa +ve (group 1) No. (%)	Hpsa +ve (group 2) No. (%)
< 20 years	3 (3.5)	7(9)
21-40 years	40(46.5)	31(39.7)
41-60 years	37(43)	28(35.9)
> 60 years	6(7)	12(15.4)
Total	86(100)	78(100)

Angioedema was recorded in only 41(30.4%) patients with chronic urticaria while 94(69.6%) patients had no angioedema and no statistical significant difference was found between patients that had positive HpSA and those had negative HpSA in group 1 (P > 0.05), (**Table-3).**

Table 3. Correlation of angioedema with Chronic urticaria

	Chronic urticaria		Total No. (%)
	Positive HpSA No. (%)	Negative HpSA No. (%)	
Positive angioedema	28 (63.4)	15 (36.6)	41 (100)
Negative angioedema	60 (63.8)	34 (36.2)	94 (100)
Total	86 (63.7)	49 (36.3)	135 (100)

P value =0.9

The duration of urticarial symptoms ranged from 2-48 months with a mean of 10.9 months. About 69 patients (51.1%) had duration of chronic urticarial symptoms less than 6 months, (Table-5). Regarding the difference in the duration of chronic urticaria no statistical difference was found between patients with positive HpSA and patients with negative HpSA in group 1 (P > 0.05), (Table-4).

Table 4. Duration of urticaria in patient with HpSA positive and negative HpSA

Duration	Chronic urticaria		Total
	Positive HpSA No. (%)	Negative HpSA No. (%)	
< 6 months	45 (65.2)	24 (34.8	69 (100)
6-12 months	28 (63.6)	16 (36.4)	44 (100)
> 12 months	13 (59.1)	9 (40.9)	22 (100)
Total	86 (63.7)	49 (36.3)	135 (100.0)

P-value=0.8

Response to eradication therapy

Only 52 patients with chronic urticaria and positive HpSA test completed six months follow up period, 47(90.4%) patients with positive HpSA achieved eradication from *H. pylori* by first line therapy while 3(5.8%) patients required second line therapy for eradication. In 2 (3.8%) patients, *H. Pylori* persisted despite two courses of eradication therapy. Complete remission (**CR**) of urticarial symptoms with no need for H1 blocker at the end of six months was observed in 30 (57.7%) patients who were eradicated from *H. pylori* while partial remission (**PR**) was recorded in 12(23.1%) patients therefore the response to eradication therapy (**CR+PR**) was evident in 42 (80.8%) patients while the remaining 10(19.2%) patients showed no objective response (**NR**), two of them had persistent *H. pylori* infection and still require antihistamine treatment daily or almost daily during the follow up period. The response of urticarial symptoms (**CR+PR**) was found to be statistically significant (P value = 0.019) after eradication of *H. pylori*, (Table-5).

Table 5. Objective response to treatment at the end of six months in patients with chronic urticaria and *H. pylori* infection

H. Pylori eradication	Objective response of chronic urticaria				Total
	Complete remission (CR)	Partial remission (PR)	Response (CR+PR)*	No response (NR)*	
Eradicated by 1st cycle	28 (59.6)	12 (25.5)	40 (85.1)	7 (14.9)	47 (100.0)
Eradicated by 2nd cycle	2 (66.7)	0 (0.0)	2 (66.7)	1 (33.3)	3 (100.0)
Not eradicated	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	2 (100.0)
Total	30 (57.7)	12 (23.1)	42 (80.8)	10 (19.2)	52 (100.0)

***P value=0.019**

Side effect of therapy

In general, no significant adverse effects was reported apart from low sedative effect of antihistamine, one patients (1.9%) developed exacerbation of urticarial rash after taking clarithromycin drug that was replaced after that by levofloxacin,[7,15] five patients (9.6%) complained from unpleasant taste of clarithromycin, three female patients (5.7%) developed vaginal discharge after receiving triple therapy and one patient (1.9%) complained from mild diarrhea after taking eradication therapy for *H. pylori*.

DISCUSSION

Chronic urticaria is a distressing problem in daily clinical practice that is difficult to deal with because of its chronic & idiopathic nature, Helicobacter pylori has been implicated in a variety of diseases other than those related to gastrointestinal tract, like chronic urticaria. [17,18] In the current study the majority of patients were mainly in 3rd and 4th decade of life which is comparable to that reported by other study,[19] indicating that chronic urticaria predominantly affect adults, which is probably attributed to the fact, that chronic urticaria requires frequent and prolonged exposure to the allergens or causative agents for full immunological reaction to develop. [20] The study also showed that 65.9% of patients with chronic urticaria were females, which is similar to that reported by other study. [21] This, is thought to be due to low level of dehydroepiandrosterone (DHEA)-S in females, where it was suggested by some authors that hormone may play a possible role in the pathogenesis of chronic urticarial.[22] The present study reported that the prevalence of *H. pylori* among the studied population was (51.1%) that is nearly similar to that reported in neighboring countries. [23] On the other hand, the prevalence of *H. pylori* among patients is statistically significantly higher than that among controls (cases = 63.7% vs control=41.9%), p value < 0.001 and odds ratio was 2.4. This indicates that those people with positive *H. pylori* have 2.4 times more likelihood to get chronic urticaria, in comparison with those who are free from *H. pylori*; this result is in agreement with that of studies in Erbil and other countries[19,20,24] One study didn't show the same finding.[25] Based on the results of this study and that of others, *H. pylori* possibly play a role in the pathogenesis of chronic urticaria because of higher prevalence of positive HpSA test among patients. Moreover, the eradication therapy of *H. pylori* that was given to subgroup of patients with chronic urticaria resulted in partial or complete relief of urticarial symptoms in (80.8%) of patients; in about 57.7% of them, the cure of urticaria was complete whereas none of them showed recurrence during the period of follow up that lasted for six months, this finding is similar to that reported by other studies, [14,16,26] confirming the correlation of *H. pylori* eradication and the clinical resolution of clinical features of chronic urticaria. Although other studies showed a conflicting result stating that *H. pylori* infection and its eradication did not significantly, affect the course of chronic urticarial. [27,28] This controversy between the results of different studies is possibly due to the difference in the methods used for the detection of *H. pylori* infection, regimen used for eradication, period of follow up, resistance and recurrence of bacterial infection after eradication. In addition, we thought that chronic urticaria in non-responder might be attributed to the mechanism by which *H. Pylori* induce urticaria or other hidden causes other than *H. pylori* infection. Moreover, it has been mentioned that *H. pylori* infection may cause production of autoantibodies that might continue even after eradication of *H. pylori* infection, which possibly explains the lack of clinical improvement after eradication therapy in some patients. [29-31] Other study suggested that *H. pylori* infection might facilitate the penetration of allergens through the gastrointestinal tract with consequent induction of IgE mediated response to certain common alimentary antigens with the development of food allergy, which ultimately results in continuation of chronic urticaria even after eradication of primary *H. pylori* infection. [32] Another finding in the present study was that the gastrointestinal symptoms was observed in 68.4% of *H. pylori* positive individuals and 38.8% of them had no gastrointestinal symptoms although they are actually had positive HpSA. The prevalence of gastrointestinal symptoms among the studied population (cases and controls) with *H. pylori*

infection found to be statistically significant (P < 0.001). Therefore, this clearly shows that the presence of gastrointestinal symptoms is significantly associated with *H. pylori* infection and increase the likelihood that *H. pylori* being implicated as a factor for having chronic urticaria among those with gastrointestinal symptoms. The study failed to demonstrate any relation between angioedema and the duration of chronic urticaria with the detection of positive HpSA testing and this might indicate that *H. pylori* infection seems neither to affect the duration of the disease nor to be a risk factor for angioedema. The study also showed that 47 (90.4%) out of 52 patients with positive HpSA achieved eradication of *H. pylori* by first eradication course and this agreed with that found by other study. [33] In those who failed to respond to treatment; multiple factors may be incriminated and possibly related to both bacterium and the host including bacterial virulence factors, resistance and patient compliance that necessitate the addition of other antibiotic in the second therapeutic course.

CONCLUSIONS & RECOMMENDATIONS

1. There was association of Helicobacter pylori infection with chronic urticaria indicates that *H. pylori* may be a risk factor for chronic urticaria
2. Eradication of *H. pylori* is a valid therapeutic option for patients with chronic urticaria and positive stool antigen test as it induces complete and partial remission in 80.8% of the cases.
3. *H. pylori* testing should be specifically done in patients with no response to usual conventional treatment for chronic ordinary urticaria or symptomatic gastrointestinal patients.
4. Studying the effect of Helicobacter pylori eradication on chronic ordinary urticaria with positive autologous serum skin test (ASST) as indicator of autoimmune process is recommended.

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