

Clinicoepidemiologic Features of Chronic Urticaria in Patients with versus without Subclinical *Helicobacter pylori* Infection: A Cross-Sectional Study of 150 Patients

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Keywords

Angioedema · Gastrointestinal symptoms · *Helicobacter pylori* ELISA · Rapid urease test · Urticaria activity score

Abstract

Background: The *Helicobacter pylori* infection is linked to chronic urticaria in nearly 60% of patients. We studied clinicoepidemiologic features in patients with chronic urticaria with and without *H. pylori* infection. **Methods:** Endoscopic antral biopsy for the rapid urease test (RUT) and histopathology, and serum IgG ELISA for *H. pylori* infection were performed in 150 patients (male:female ratio 1:2.4) of chronic urticaria aged 18–68 years. Clinicoepidemiologic features including age, gender, age of onset and duration, frequency and distribution of wheals, urticaria severity score, and systemic symptoms were analyzed in patients with and without *H. pylori*. The results of serum IgG ELISA for *H. pylori* were compared with 106 age- and gender-matched healthy adult controls. **Results:** The RUT in 84 patients (56%), histopathology in 76 patients (50.6%), and *H. pylori* IgG ELISA in 94 patients (62.6%) were positive. *H. pylori* IgG ELISA was positive only in 35 (33%) controls, suggesting that chronic urticaria patients were more likely to have asymptomatic *H. pylori* in-

fection than normal controls. Although not statistically significant, patients with *H. pylori* had a higher mean urticaria severity score, number of urticaria/angioedema episodes per year, and involvement of more body sites, particularly the scalp, palms, and soles. The constitutional or gastrointestinal symptoms were statistically higher in patients with *H. pylori* infection than those without it. **Conclusion:** A subset of chronic urticaria patients appears to have asymptomatic *H. pylori* infection. However, its implications in chronicity, recurrences, the severity of urticaria, other systemic manifestations, and management remains conjectural in view of 33% of controls also having positive *H. pylori* ELISA and the endemicity of infection in developing countries.

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Introduction

Chronic urticaria, urticarial wheals, and/or angioedema of more than 6 weeks duration affects 15–20% of the population at least once during their lifetime and signifi-

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cantly affects quality of life. It affects women more often than men and usual onset is between 20 and 40 years of age [1–3]. Its etiology often remains unestablished despite extensive investigative workup rendering cause-specific management difficult. Foods, drugs, inhalants, systemic diseases, autoimmunity, and stress have frequently been implicated [4]. Focal bacterial and viral and parasitic infections have also been implicated at a rate as high as 43% of urticaria patients, and treating them empirically remains an unsubstantiated method in urticaria management [5, 6]. *Helicobacter pylori* infection has also been linked to chronic urticaria wherein it has been implicated in 60% of chronic urticaria patients in one study, while associated gastritis was present in about 71% of 68 patients in another study [7–9]. Although it may not establish a causal relationship, *H. pylori* eradication treatment leads to the remission of urticaria in up to 80% of patients, including antihistamine-unresponsive cases [7, 9–13]. A recent meta-analysis of studies comparing the prevalence of *H. pylori* infection in chronic urticaria patients and controls suggested that *H. pylori* infection is significantly, though weekly, associated with an increased risk of chronic urticaria [14]. In contrast, studies have found that evidence for a reported benefit of *H. pylori* eradication was weak and conflicting, eradication therapy may itself trigger urticaria, and the stated benefits might have been from eradication of other undiagnosed/asymptomatic infections [15, 16].

Various mechanisms have been speculated to explain the possible association of *H. pylori* with chronic urticaria [9–11, 16–18]. *H. pylori* is suggested to increase the secretion of gastric acid and pepsin, which induces active inflammation in the gastrointestinal tract leading to the recruitment of neutrophils, eosinophils, and lymphocytes, which release a family of histamine-releasing factors that induce mast cell degranulation. This might also facilitate the absorption of antigens or unmasking of existing antigens triggering urticaria. *H. pylori* as an antigen may also induce the expression of certain epitopes on endothelial cell adhesion molecules. *H. pylori* is also speculated to produce IgE antibodies by its cross-reaction with parietal cells that may encourage the release of histamine in the skin, causing wheal formation [2, 19]. The antibodies (IgG, IgA) also demonstrated against 19-kDa *H. pylori* protein probably contribute to the pathogenesis of chronic urticaria by excessive consumption of complement. Juhlin [20] suggested that impairment of both food processing and mucosal barrier function of the alimentary tract due to *H. pylori* infection perhaps creates conditions for food allergens to enter the blood stream facili-

Table 1. UAS

<i>Pruritus severity score</i>	
Absent	0
Present but not disturbing	1
Disturbing but not hampering daytime activity or sleep	2
Hampering daytime activity or sleep	3
<i>Wheal score (average number of wheals in 24 h)</i>	
<10 wheals	1
10–50 wheals	2
>50 wheals	3
Involving almost the whole body	4

Urticaria activity score (UAS) = pruritus severity score + wheal score. Grading: mild = UAS up to 2; moderate = UAS of 3–5; severe = UAS of 6–7.

tated by inflammatory lesions of the intestinal tract. However, its significance in severity, recurrences, and chronicity of urticaria remains uncertain and lacks consensus in general as *H. pylori* is also considered to be gastrointestinal commensal, and prevalence did not differ from that of control groups in some of the studies [21–25]. We performed this study with the objective of studying clinicoepidemiologic features in patients with chronic urticaria with or without *H. pylori* infection. The information will have a bearing on prescriptions of antihistamines in super pharmacologic doses or other immunomodulating drugs in the long-term management of urticaria, as their use based on clinical symptoms alone may sometimes be considered unjustified.

Materials and Methods

One hundred and fifty patients (male:female ratio 43:107) aged 18–68 years with chronic urticaria, and 106 age- and gender-matched healthy adult controls (male:female ratio 31:75) not on any medication were studied during April 2015 and March 2016. Patients with physical urticaria, urticarial vasculitis, acute urticaria, concomitant medical and surgical diseases contraindicating upper gastrointestinal endoscopy, treatment with proton pump inhibitors/antibiotics in the preceding 4 weeks, as well as pregnant or lactating women were excluded from the study. Subjects with systemic diseases/infections known to cause urticaria and physical urticaria were excluded by detailed clinical history/examinations, provocation tests, and other relevant investigations, such as complete hemogram, thyroid and hepatorenal function tests, fasting blood glucose estimation, ASO titer, rheumatoid factor, HbsAg, urinalysis, and stool microscopy for ova/cysts. The urticaria activity was graded as mild, moderate, and severe on the basis of the modified urticaria activity score (UAS; Table 1) [26]. An episode of urticaria was defined as several days of urticaria signs and symp-

Table 2. Baseline characteristics of patients and controls

		Patients (n = 150)	Controls (n = 106)	OR
Gender	Males	43 (28.7)	31 (29.2)	–
	Females	107 (71.3)	75 (70.8)	–
	Male:female ratio	1:2.4	1:2.4	–
Age	Range (mean ± SD), years	18–68 (38.9±10.9)	18–60 (36.9±10.6)	
	18–30 years	35 (23.3)	36 (34)	–
	31–40 years	55 (36.7)	35 (33)	–
	41–50 years	36 (24)	23 (21.7)	–
	51–60 years	20 (13.3)	12 (11.3)	–
	61–70 years	4 (2.7)	0	–
Duration	Range (mean ± SD), months	1.5–300 months (40.8±61.5)		
	1.5–12 months	76 (50.7)	–	–
	13–24 months	24 (16)	–	–
	25–36 months	13 (8.7)	–	–
	37–48 months	10 (6.6)	–	–
	≥49 months	27 (18)		
Age of onset	Range (mean ± SD), years	8–68 (35±12)		
	≤10 years	3 (2)	–	–
	11–20 years	6 (4)	–	–
	21–30 years	46 (30.7)	–	–
	31–40 years	44 (29.3)	–	–
	41–50 years	37 (24.7)	–	–
	51–60 years	11 (7.3)	–	–
	>60 years	3 (2)	–	–
Positive results for <i>H. pylori</i> ¹	RUT	84 (56)	–	–
	Histopathology	76 (50.6)	–	–
	Serum IgG ELISA	94 (62.6)	35 (33)	3.39 (2.15–5.76)

Data are presented as *n* (%) or as indicated. RUT, rapid urease test; OR, odds ratio.

¹ Some patients have 2 or more positive results: 1 test was positive in 126 patients, 2 tests in 93 patients, and 3 tests in 35 patients.

toms with intervening asymptomatic and urticaria-free days. All patients were subjected to an upper gastrointestinal endoscopic examination, and antral biopsy for rapid urease test (RUT) and histopathology to detect *H. pylori* infection. Serology for *H. pylori* IgG antibodies was performed as per the manufacturer's instructions using ELISA kits from Calbiotech Life Science Co. (El Cajon, CA, USA), with 94% sensitivity and 93% specificity. The controls were only subjected to ELISA for *H. pylori* IgG antibodies for ethical reasons and the seropositivity rates were then compared with those in urticaria patients. The patients were divided into 4 groups for the comparison of clinicoepidemiologic features on the basis of the results of tests for *H. pylori*. Group A included patients who tested positive for all 3 tests, group B patients had 2 positive tests, and group C patients had 1 positive test. All test results in group D patients were negative. The χ^2 test, odds ratio (OR), paired *t* test, Fisher exact tests, and 1-way ANOVA test were used for the statistical analysis using the Epi Info software of the Centers for Disease Control and Prevention (CDC). A *p* value <0.05 calculated at the 5% level (95% confidence limit) was considered statistically significant.

Results

The baseline clinicodemographic and investigative data for *H. pylori* of all patients and controls are shown in Table 2. The majority (55; 36.7%) of patients were aged between 31 and 40 years, and women outnumbered men by a factor of almost 2.5. The duration of urticaria was 6 weeks to 300 months (mean ± SD 40.81 ± 61.48 months) and the majority (76; 50.7%) of the patients had urticaria for less than 12 months. The age at onset of urticaria ranged from 8 to 68 years (mean ± SD 35 ± 12) and in 90 patients (60%) it was 21–40 years. The RUT was positive in 84 (56%), histopathology was positive in 76 (50.6%), and *H. pylori* IgG ELISA was positive in 94 patients (62.6%). There were 35, 58, 33, and 24 patients in groups A, B, C, and D, respectively. Table 3 depicts the comparative clinicoepidemiologic features of patients in all 4 groups who showed no

Table 3. Comparison of characteristics of urticaria patients in group A and group B

		Group A: 3 positive tests (n = 35)	Group B: 2 positive tests (n = 58)	Group C: 1 positive test (n = 33)	Group D: 3 negative tests (n = 24)	p value
Gender distribution	Males	10 (28.6)	16 (27.6)	10 (30.3)	7 (29.2)	
	Females	25 (71.4)	42 (72.4)	23 (69.7)	17 (70.8)	
	Male:female ratio	1:2.5	1:2.6	1:2.3	1:2.4	
Age, years	Range	24–64	18–62	21–68	20–63	0.255
	Mean ± SD	38.08±10.53	39.62±10.81	41.06±9.96	35.5±12.59	
Age at onset, years	Range	9–63	10–61	8–68	16–60	0.410
	Mean ± SD	34.88±11.01	36.44±11.26	36.77±12.32	32.04±13.47	
Duration of urticaria, months	Range	2–240	1.5–300	1.5–288	2–144	0.678
	Mean ± SD	39.22±62.95	37.78±61.72	52.22±72.18	34.70±41.08	
Previous urticaria episodes ¹	0	10 (28.6)	14 (24.1)	7 (21.2)	6 (25)	0.395
	1–60	19 (54.3)	23 (39.7)	14 (42.4)	9 (37.5)	
	61–120	5 (14.3)	18 (31)	12 (36.4)	8 (33.3)	
	121–180	0	0	0	1 (4.2)	
	181–240	1 (2.8)	3 (5.2)	0	0	
	Mean ± SD	39.94±51.35	58.01±61.15	44.87±44.39	54±50.08	
Episodes of urticaria with angioedema ¹	0	22 (62.9)	33 (56.9)	19 (57.6)	15 (62.5)	0.254
	1–10	13 (37.1)	18 (31.1)	11 (33.3)	6 (25)	
	11–20	0	5 (8.6)	2 (6.1)	2 (8.3)	
	21–30	0	2 (3.4)	1 (3)	1 (4.2)	
	Mean ± SD	1.2±2.08	3.72±7.34	3.12±5.87	3.58±6.82	
UAS	2	2 (5.7)	2 (3.4)	1 (3.0)	0 (0)	0.934
	3	5 (14.3)	5 (8.6)	2 (6.1)	2 (8.3)	
	4	3 (8.6)	12 (20.7)	6 (18.2)	4 (16.7)	
	5	8 (22.9)	15 (25.9)	8 (24.2)	9 (37.5)	
	6	4 (11.4)	10 (17.3)	7 (21.2)	4 (16.7)	
	7	13 (37.1)	14 (24.1)	9 (27.3)	5 (20.8)	
	Mean ± SD	5.31±1.65	5.17±1.41	5.36±1.38	5.25±1.22	
Body sites involved	1	0 (0)	1 (1.8)	0 (0)	1 (4.2)	0.174
	2	8 (22.9)	17 (29.3)	12 (36.4)	9 (37.5)	
	3	15 (42.9)	17 (29.3)	10 (30.3)	8 (33.3)	
	4	4 (11.4)	11 (19)	6 (18.2)	6 (25)	
	5	3 (8.6)	6 (10.3)	3 (9.1)	0 (0)	
	6	4 (11.4)	6 (10.3)	1 (3)	0 (0)	
	7	1 (2.8)	0 (0)	1 (3)	0 (0)	
Site affected by wheals	Mean ± SD	3.51±1.40	3.37±1.33	3.21±1.29	2.79±0.88	
	Trunk	35 (100)	58 (100)	33 (100)	24 (100)	
	Limbs	35 (100)	57 (98.3)	33 (100)	23 (95.8)	
	Face	17 (48.6)	34 (58.6)	17 (51.5)	15 (62.5)	
	Scalp	18 (51.4)	22 (37.9)	9 (27.3)	4 (16.7)	
	Mouth/tongue	1 (2.8)	3 (5.2)	1 (3)	0 (0)	
	Palms	10 (28.6)	17 (29.3)	8 (24.2)	2 (8.3)	
	Soles	6 (17.1)	7 (12.1)	5 (15.1)	0 (0)	

Data are presented as n (%) or as indicated. A p value <0.05 was considered statistically significant. UAS, urticaria activity score.

¹ A total of 126 (84%) patients with positive *H. pylori* tests and 24 (16%) patients with negative tests had multiple recurrent episodes of urticaria and/or angioedema.

Table 4. Comparison of systemic symptoms in group A and group B patients

	Group A (n = 35)	Group B (n = 58)	Group C (n = 33)	Group D (n = 24)	p value
Symptomatic patients	23 (65.7)	43 (74.1)	30 (90.9)	15 (62.5)	
Symptoms					
1–3	11 (31.4)	25 (43.1)	11 (33.3)	7 (29.2)	
4–6	11 (31.4)	9 (15.5)	11 (33.3)	6 (25)	
7–9	1 (2.8)	5 (8.6)	6 (18.2)	1 (4.2)	
>9	0	4 (6.9)	2 (6.1)	1 (4.2)	
Mean ± SD	2.28 ± 2.26	3 ± 3.28	4.42 ± 2.95	2.37 ± 2.96	0.015
Gastrointestinal symptoms	11	14	16	5	
Nausea	4	3	7	1	
Vomiting	2	0	3	0	
Abdominal pain	5	10	12	2	
Diarrhea	1	3	3	0	
Indigestion	2	4	7	2	
Cardiorespiratory symptoms	15	25	21	8	
Syncope	2	10	10	2	
Flushing	8	20	10	4	
Breathlessness/wheeze	4	5	6	1	
Palpitations	6	13	7	5	
Joint symptoms	3	6	5	4	
Joint swelling	1	2	4	2	
Joint pain	3	6	4	4	
General symptoms	20	34	25	13	
Malaise	6	12	10	4	
Loss of concentration	9	24	18	8	
Headache	6	12	10	4	
Lassitude	6	17	13	6	
Feverish sensation	1	9	6	3	
Feeling of hot or cold	11	13	12	5	

Data are presented as *n* (%) or as indicated. Most patients had multiple symptoms. A *p* value <0.05 was considered statistically significant.

statistically significant difference in age, gender, age at onset, and duration of urticaria. The mean number of recurrences of urticaria and/or angioedema was 39.94 ± 51.35 , 58.01 ± 61.15 , 44.87 ± 44.39 , and 54.50 ± 50.08 episodes per year in group A, B, C, and D, respectively. The groups were statistically comparable for the number of episodes of urticaria and/or angioedema. Multiple body sites were involved by urticarial wheals in all patients; the trunk was the most frequent site involved followed by limbs and the face/scalp in all 4 groups. The involvement of the scalp, mouth, tongue, palms, and soles was less frequent in group D patients by comparison. The mean UAS values (5.31 ± 1.65 , 5.17 ± 1.41 , 5.36 ± 1.38 , and 5.25 ± 1.32 in group A, B, C, and D patients, respectively) were also comparable statistically. However, it was observed that of 133 patients with a moderate to severe UAS, 109 (81.95%) were positive for *H. pylori* and had a greater mean number of episodes of urti-

caria and/or angioedema per year. Also, the mean number of sites involved in group D patients was less as compared to those in the other 3 groups.

One to more than 9 systemic symptoms were present in 23 (65.7%), 43 (74.1), 30 (90.9%), and 15 (62.5%) patients in groups A, B, C, and D, respectively (Table 4). A higher number of patients in groups A, B, and C experienced gastrointestinal symptoms including diarrhea and abdominal pain (in 41 vs. 5 patients), or general symptoms such as malaise, loss of concentration, lassitude, headache, a feverish sensation, and feeling hot or cold (in 79 vs. 13 patients), and cardiorespiratory symptoms like breathlessness, flushing, and palpitations (in 61 vs. 8 patients), and joint pains (in 14 vs. 5 patients). Overall, the mean number of symptoms were significantly higher ($p < 0.05$) in more patients with positive than with negative test results (96 vs. 15).

Discussion

The demographic profile of the 150 patients in this study corroborates with descriptions in the dermatology literature [1–3]. An etiopathogenetic link between *H. pylori* infection and chronic urticaria and possible improvements after its eradication has been demonstrated. Chiu et al. [27] studied 25 patients with chronic urticaria and detected *H. pylori* in 14 (56%) patients, suggesting its possible role in the course of chronic urticaria irrespective of different virulent genotypes. Sadighha et al. [9] noted that IgG antibodies against *H. pylori* were positive in 74.6% of 75 chronic urticaria patients as compared to 56% of the control group. Valsecchi and Pigatto [17] reported a high prevalence of *H. pylori* infection in chronic urticaria patients by circulating IgG antibodies against the bacterium and positive urea breath tests in 62% of cases. In our study, RUT was positive in 84 patients (56%), histopathology in 76 (50.6%), and *H. pylori* IgG ELISA in 94 (62.6%). In comparison, *H. pylori* IgG ELISA was positive in only 35 controls (33%), suggesting that the chronic urticaria patients were more likely to harbor *H. pylori* infection than normal controls (OR 3.39, 95% CI 2.15–5.76). However, the significance of *H. pylori* in etiopathogenesis or severity of chronic urticaria remains debatable. The severity of urticaria varies and is often more severe in patients with *H. pylori* infection and said to improve or show a better therapeutic response to antihistamines after eradication therapy. However, researchers have also shown no significant etiologic correlation between the two, or therapeutic improvement of urticarial symptoms following eradication therapy [21–24]. Abdou et al. [10] assessed the prevalence of *H. pylori* infection in 35 patients of chronic urticaria and 10 normal control subjects. They did not find a statistically significant difference for the presence of *H. pylori* in the 2 groups (57 vs. 40%). Nevertheless, the severity of urticarial symptoms was greater in 20 *H. pylori*-positive patients than in 15 *H. pylori*-negative patients. We also made similar observations wherein it was noted that of 133 patients with a moderate UAS (3–5) to severe UAS (6–7), 109 (81.95%) were positive for *H. pylori* and had a greater mean number of episodes per year of urticaria and/or angioedema and sites involved when compared with group D patients. However, a greater number (96 vs. 15) of patients with positive test results had a significantly higher ($p < 0.05$) mean number of systemic symptoms than patients with negative results. Furthermore, the prevalence of *H. pylori*-associated gastrointestinal symptoms remains variable, from being symptomatic to the complete absence of

symptoms [2, 8, 10, 28]. In their 57% urticaria patients with positive *H. pylori*, Abdou et al. [10] reported no gastric symptoms. In contrast, Wedi et al. [8] noted a high prevalence of *H. pylori* gastritis and 47% of patients showed elevated *H. pylori*-specific IgA and/or IgG antibodies. In our 126 patients with positive *H. pylori* tests, only 41 (32.5%) had gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, diarrhea, or indigestion, while the majority (85, 67.5%) were completely asymptomatic, making the clinical detection of this infection difficult. Overall, the urticaria activity was higher with a statistically significant association of systemic symptoms and involvement of the scalp, palms, and soles in patients with *H. pylori* infection compared to patients without it.

Limitations

The cross-sectional nature of study and absence of assessment of urticaria activity after *H. pylori* eradication are the main limitations of this study. Also, the control group could not be subjected to endoscopy for RUT and histopathologic analysis. The worldwide endemic nature of *H. pylori* infection, particularly in developing countries with a low socioeconomic status, poor sanitation and water hygiene, and overcrowding remains another confounding factor.

Conclusion

A subset of patients with chronic urticaria possibly harbors asymptomatic *H. pylori* infection. How it influences the chronicity, recurrences, severity, or other manifestations of urticaria/angioedema, and its remission after eradication therapy, remains conjectural given that 33% of controls were also *H. pylori* ELISA-positive and the high endemicity of infection in developing countries in general. More systematic and better-designed future studies with a large number of patients and long-term follow-up may perhaps resolve some of these issues.

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Ethics Statement

The study was approved by the Institutional Scientific Protocol Review Committee and Institutional Ethics Committee (Rgn No. ECR/490/Inst/HP/2013). Informed consent was obtained from all patients enrolled in the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Disclosure Statement

The clinical data form part of a thesis submitted to Himachal Pradesh University, Shimla, India, for the degree of MD. All authors declare that they have no competing interests and therefore

nothing else to declare, and have contributed significantly and take full responsibility for the manuscript. The authors confirm that this paper has not been previously published.

Author Contributions

S.K. obtained, compiled, and analyzed all data and prepared the initial draft. V.K.M. analyzed and interpreted the data, drafted and critically evaluated the manuscript for important intellectual content. B.S.R. assisted with gastrointestinal endoscopic procedures and interpreted the findings. R.K.R. interpreted histopathologic features of antral biopsies. K.S.M., P.S.C., R.R., and V.S. helped with data compilation and the literature search. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

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