

Report

Helicobacter pylori and idiopathic chronic urticaria

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Abstract

Background Different studies have shown a high prevalence of *Helicobacter pylori* (HP) infection in patients with chronic urticaria (CU), and occasional remission of the skin lesions after eradication therapy. Recent investigations, however, have failed to find a significant relationship between the two conditions. We designed a case–control study to assess the prevalence of HP infection and the effect of bacterium eradication on the outcome of the skin disease in patients affected by CU. The literature is reviewed.

Methods Twenty-five patients diagnosed with CU were included. Information about their medical history and a complete laboratory investigation ruled out other diseases or situations suspected to cause CU. Twenty-five healthy volunteers from a census-based, randomized sample were used as controls. HP infection was assessed by the ¹³C-urea breath test (UBT). Eradication therapy included oral amoxicillin, omeprazole, and clarithromycin for 1 week.

Results The high prevalence of HP infection (68%) and mean titer of UBT (24.13) in our patients with idiopathic CU do not differ from the general population. Marked differences were observed in the mean age of the CU patients with positive UBT (45.52 years) vs. those without HP infection (35.25 years). After eradication therapy, only one patient showed a complete remission of urticaria and two showed a partial remission.

Conclusions Our results support a lack of relationship between HP infection and the course of idiopathic CU.

Introduction

At present, *Helicobacter pylori* (HP) is considered probably the most common chronic bacterial infection in humans. It is now generally accepted that HP infection plays an etiologic role in the development of chronic active gastritis, peptic ulcer disease, gastric malignancy, and low-grade gastric mucosa-associated lymphoid tissue lymphoma.

Chronic urticaria (CU) is a common clinical disorder with a complex pathophysiologic mechanism. Although not clearly confirmed, hidden or overt bacterial, viral, fungal, and protozoan agents have been reported as possible initiating factors.¹ Nevertheless, no etiologic factor has been found in a large number of patients, which makes idiopathic chronic urticaria (ICU) a major problem for both physicians and patients. Recent observations have shown a high prevalence of HP infection in patients with CU, and occasional remission of the cutaneous signs and symptoms after eradication therapy, suggesting a possible

etiopathogenetic role of HP in some cases;^{2–8} however, a considerable number of publications have failed to find a significant relationship between the two conditions.^{9–16} This controversy has been aided by the large variability in the methodologic methods applied between the studies (type and duration of eradication therapy, follow-up after treatment, diagnostic methods of HP infection before and after treatment, criteria for the type of response of urticarial lesions, etc.), by the evaluation of HP infection with reference to the overall prevalence in the different countries, without considering the wide variability of percentages among different areas of the same country, or even between different areas of the same city, and, exceptionally, case–control studies have been performed in terms of prevalence.⁸

Given these considerations, and in an attempt to clarify the possible role of HP in the pathogenesis of ICU, we decided to contribute by designing a case–control study of a population-based sample to assess the prevalence of HP

Table 1 Frequency of positivity and titer of the ^{13}C -urea breath test in idiopathic chronic urticaria patients vs. controls

	Positive ^{13}C -UBT, No./ No. of patients (%)	^{13}C -UBT mean titer (SD)
Patients	17/25 (68%)	24.13 (21.71)
Controls	21/25 (84%)	24.36 (17.62)
P	0.32	0.96

UBT, urea breath test; SD, standard deviation.

infection and the effects of bacterium eradication on the outcome of the skin disease in patients affected by ICU. We also reviewed the literature.

Patients and methods

Study population

Twenty-five unselected patients (17 women and 8 men) from our outpatient clinic diagnosed with ICU, seen during the period from December 1996 through to January 1998, were studied. The patients' ages ranged from 22 to 67 years (mean, 42.2 years). The setting of the study was a university hospital in Madrid that renders a service to a population from the center and suburbs. Information about the occupational activity, medical history, frequency of flares, history of atopic diseases, presence of any concomitant or past gastrointestinal disease or complaints, drug intake, and tobacco and alcohol consumption was taken. Investigation for physical triggers and focus of infection in various locations was performed when indicated by the patient's history. Each patient was studied according to a protocol that included a complete blood count with a differential analysis, erythrocyte sedimentation rate (ESR), complete blood biochemistry, urine analysis, protein electrophoresis, total serum immunoglobulin E (IgE), fecal examinations for ova and parasitic disease, cryoglobulins and cold agglutinins, antinuclear antibodies (ANA), rheumatoid factor, C3, C4, serum tests for hydatidosis, hepatitis C virus (HCV), hepatitis B virus (HBV), syphilis, Epstein-Barr virus, and mycoplasma. ICU was defined as the occurrence of wheals of more than 6 weeks' duration and when no other disease or situation associated with CU was detected. Prescription of H1 antihistaminic drugs and corticosteroids was continued during the study. Exclusion criteria included oral antimicrobial therapy, omeprazole, sucralfate, or bismuth-containing drugs in the preceding 4 weeks, previous gastrectomy, and current gastroscopy.

Twenty-five apparently healthy volunteers (17 women and 8 men; mean age, 42.2 years) were used as controls. They were taken from a census-based, randomized sample from the same geographic area. All patients and controls were informed about the study and consented to participate.

Urea breath test (UBT)

All patients and controls were examined for HP infection with the ^{13}C -UBT at the Gastroenterology Department of the Hospital Universitario de la Princesa. After the subject had fasted for at least 6 h, 20 mL 0.1 N citric acid containing 100 mg [^{13}C]-urea (Tau-Kit®, Isomed SL, Madrid) was orally administered. Breath samples were collected before and 30 min after ingestion of the tracer. The ratio of ^{13}C to ^{12}C (δ value) of the expired breath was measured with a mass spectrometer. Results were expressed as change per thousand ($\delta\%$). A change over baseline of more than 5 $\delta\%$ indicated HP infection.

Eradication therapy

Eradication therapy was offered to patients with positive UBT. Fifteen patients who agreed to participate were treated orally with omeprazole (20 mg twice daily) amoxicillin (1 g twice daily) and clarithromycin (500 mg twice daily) over a period of 1 week. Six weeks after the end of eradication therapy, the patients underwent a UBT in order to check whether or not the eradication had been successful. The clinical evaluation and follow-up were provided by the same physician (ED) for at least 12 months from eradication. The results were documented as: complete remission (absence of flares), partial remission (more than 50% improvement), slight improvement (less than 50%), no change, or aggravation.

Statistical analysis

To study the association between ICU and the result of UBT, χ^2 was used. To study the means of the numerical variables between the patients and controls, Student's *t*-test was applied.

Results

Twenty-five patients diagnosed with ICU were enrolled in the study. The duration of disease extended from 2 months to 10 years. Ten patients mentioned present or past gastrointestinal symptoms. Thirteen patients were receiving treatment with H1 antihistamines and five with corticosteroids. Laboratory tests revealed no significant evidence of other underlying diseases. A moderate elevation of total IgE was found in four patients (range, 150–398 U/mL; upper normal limit, 120 U/mL) and a slightly elevated ANA titer in two patients (1/40 and 1/80).

There were no statistically significant differences between the ICU patients and the controls, either in the frequency of UBT positivity or the UBT titer (Table 1). The mean duration of disease was also similar between the UBT-positive group (25.52 months) and the UBT-negative group (22.87 months). Marked differences, near statistical

Table 2 Studies about the frequency of HP infection and effect of eradication therapy in patients with chronic urticaria

Reference	No. of cases	City (country)	Design of the study	Eradication therapy (days)	Follow-up after treatment (months)	HP-positive cases (%)
2	30	Bratislava (Slovakia)	Open prospective	Amox, tet, Metr, Bis (28)	3	21 (70)
3	7	Genoa (Italy)	Open prospective	NM	NM	4 (57.1)
4	10	Minden (Germany)	Open prospective	Amox, Om (14)	3	8 (80)
5	25	Berlin (Germany)	Open prospective	Amox, Clar, Tet, Metr, Bis, Om (14–28)	2.5	17 (68)
6	42	Rome (Italy)	Open prospective, control study	Amox, Clar, Lans (7)	3	23 (55)
7	100	Hannover (Germany)	Open prospective	Amox, Clar, Metr, Om (7), Bis, Tet	≤ 3	47 (47) ^b
10	85	Vienna (Austria)	Prospective, randomized, double-blind, placebo-controlled	Amox, Metr (12)	4	39 (47)
11	55	Nürnberg (Germany)	Open prospective, control study	Clar, Metr, Om (7)	16	25 (56) ^c
12	35	Istanbul (Turkey)	Open prospective	Amox, Clar, Om (7)	NM	27 (77)
13	125	Bergamo, Milan (Italy)	Prospective, randomized, control study	Clar, Metr, Om (7)	12	78 (62)
15	50	Bern (Switzerland)	Prospective, double-blind placebo-controlled	Amox, Lans (14)	2	12 (24)
16a	188	Münster (Germany)	Open prospective	Amox, Om (14)	6	30 (15.9)
8	18	Porto Alegre (Brazil)	Open prospective, case-control study	Amox, Metr, Om	NM	12 (66.7)
This study	25	Madrid (Spain)	Open prospective, case-control study	Amox, Clar, Om (7)	≥ 12	17 (68)

Table 2 (cont.)

Reference	Diagnostic method	No. erad. ther./ confirmed erad. (%)	Course of CU after eradication therapy					
			Eradicated		Non-eradicated		Controls HP(+)	
			CR	PR	CR	PR	CR	PR
2	G + B, culture, UT	21/21 (100%)	20/21 (95%)	—	—	—	—	—
3	NM	4/NM	3/4 (75%)¶	—	—	—	—	—
4	G + B, UT	8/NM	8/8 (100%)¶	—	—	—	—	—
5	G + B, ¹³ C-UBT, serum IgG	17/14 (82%)	8/14 (57%)**	6/14 (42%)	0/3	0/3	—	—
6	¹³ C-UBT	18/16 (88%)	13/16 (81%)	3/16 (18%)	0/2	0/2	—	—
7	G + B, UT, serum IgG/IgA	24/21 (87%)	14/21 (66%)	5/21 (23%)	1/2 (50%)	1/2 (50%)	4/18 (22%)	5/18 (27%)
10	G + B, UT	11/10 (90%)	††	—	—	—	—	—
11	G + B, UBT	17/NM	8/17 (47%)¶	—	—	—	4/8 (50%)	—
12	G + B, UT	27/17 (73%)§	5/17 (29%)	—	2/6 (33%)	—	—	—
13	G + B, ¹³ C-UBT, serum IgG	31/29 (93%)	3/31 (9%)¶	—	—	—	1/34 (3%)	—
15	¹³ C-UBT, serum IgG	11/3 (27%)	1/3 (33%)	—	3/8 (33%)	—	—	—
16*	¹³ C-UBT	30/24 (80%)	6/24 (25%)	2/24 (8%)	—	—	—	—
8	Serum IgG	12/NM	6/12 (50%)	4/12 (33%)	—	—	—	—
This study	¹³ C-UBT	15/12 (80%)	1/12 (8%)	2/12 (16%)	—	—	—	—

HP, *Helicobacter pylori*; NM, not mentioned; CR, complete remission; PR, partial remission; CU, chronic urticaria; G + B, gastroscopy and biopsy; Ig, immunoglobulin; UBT, urea breath test; UT, urease test.

*Chronic urticaria and/or angioedema. †47/100 seropositive for HP, 26/27 who underwent gastroscopy had antral HP infection. ‡25/44 (56%) as 11 patients from the 55 were not HP investigated. §No control gastric biopsy in four patients. ¶Not mentioned whether eradicated or not. **> 75% improvement. ††No difference between eradication therapy and placebo (data not shown).

significance ($P = 0.06$), were observed in the mean age of the ICU patients with positive UBT (45.52 years) and those without HP infection (35.25 years). Of the five patients who were being treated with corticosteroids, four had a positive UBT (80%) with a UBT mean titer of 42.64, much higher than that from the ICU group.

Fifteen patients with HP infection were treated orally with triple therapy. At the post-treatment evaluation, 12 patients were HP eradicated. Six showed no significant change in their urticaria, three had an initial slight improvement (lesser duration and less severe flares), but returned to pre-eradication symptoms even though UBT was still negative in subsequent tests, two had a partial and prolonged remission, and one showed complete remission. This last patient had ICU of 8 months' duration not previously controlled with antihistamines. He had associated diabetes mellitus but no gastrointestinal disease. The patient is still free of lesions 20 months since HP eradication. The three patients without eradication showed no change in their urticarial wheals during the follow-up period.

Discussion

The consideration of HP as a major pathogenetic factor in gastrointestinal diseases has been followed by an increasing reference to the association of HP with numerous extra-digestive pathologies,¹⁷ with a considerable number of dermatologic conditions among them.^{18–31} The first reports in the literature about the association of HP infection with CU were promising. The high prevalence of HP infection in this series, ranging from 55% to 80%, and particularly the high success rate of CU clinical remissions in HP-positive patients after eradication therapy, ranging from 95% to 100%,^{2–6} encouraged new studies to confirm these results, and seemed to have uncovered part of the explanation of the etiology of ICU (Table 2). The possible role of HP as an etiopathogenetic agent, at least in some cases of ICU, seemed a reality. The mechanisms that might explain such an association were related to immunologic reactions to antigens of HP. The induction of a specific IgE immune response or the intervention of several inflammatory mediators released during the immunologic reaction might participate in the pathogenesis of urticarial lesions.^{6,32} Most of the more recent studies, however, have failed to support such an association,^{10–13,15,16} indicating a controversy not yet resolved³³ (Table 2). The relatively small number of cases in some series, the highly variable conditions of the studies in terms of diagnostic tools for HP detection and type of eradication therapy, and the short follow-up, mainly in the first reports, have probably contributed to this confusion. A possible difference in the

antigenicity or biological activity of the bacterium in different countries has even been argued as a possible reason for this discrepancy. Only one case-control study has been performed to evaluate the prevalence,⁸ and very few controlled studies, limited by a relatively small number of patients, have attempted to evaluate the effect of eradication therapy on the course of the skin disease. Schrutka-Koelbl *et al.*,¹⁰ through a prospective, randomized, double-blind study on 85 patients, obtained 47% HP-positive cases, but found no difference in the outcome of urticarial lesions between the patients treated with eradication therapy and the placebo group. Valsecchi and Pigatto¹³ performed a prospective, randomized, control study on 125 patients. After 12 months of follow-up, they found no influence of eradication, as there were no clear differences in the clinical response of skin lesions between those HP-positive patients submitted to triple therapy, HP-negative patients who also received triple therapy, and HP-positive patients not given this treatment. Finally, Schnyder *et al.*,¹⁵ in a double-blind, placebo-controlled, cross-over study on 46 patients, found only 24% HP-positive patients and, of the three patients eradicated, only one showed a complete remission of CU. Other open prospective studies have shown clinical remissions ranging from 26.7% to 29.5%,^{12,16} probably related to the spontaneous remission of lesions, far from the promising results of the former publications.

In our study, we found no differences between the ICU patients with and without HP infection and the control group regarding the prevalence of gastric HP, titer of UBT, and duration of the disease. The difference between the mean age of the ICU patients with positive UBT vs. those with negative UBT can be explained by the influence of age on the HP infection rate (prevalence of HP infection increases with age³⁴). The high UBT titer in those patients receiving treatment with corticosteroids might indicate the role of these drugs in favoring HP gastric colonization. Although there is some controversy, several reports consider that ¹³C-UBT enables a semiquantitative assessment of the extent of HP colonization in the stomach.^{35–38} Nevertheless, the limited number of cases restrict any conclusion about this. Our results on the response of ICU lesions after eradication therapy are disheartening. The complete remission in one patient and the partial remission in two do not support a relationship between HP infection and ICU. Considering the natural course of CU and its relatively high spontaneous remission rate (6% for CU of more than 6 months;³⁹ 25% of 20 patients who did not benefit from eradication therapy and 43% of eight patients who did not have HP infection occurring after an average time of 4.8 and 4 months, respectively;¹² or 41% within 6 months¹⁵), our results could be explained in these terms.

Conclusions

Our results and the critical review of the literature indicate that the pathogenetic role of HP in ICU is highly doubtful. Although the possible contribution of HP to some limited cases of CU cannot be ruled out, the need for large-scale, randomized, double-blind, clinical trials in several countries with different prevalences is mandatory.

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Mistress of the house, Oak Alley Plantation,
by Derry L. Scholnick, MD.
Honorable mention, Photography.
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