

Beneficial Effects of *Helicobacter pylori* Eradication on Idiopathic Chronic Urticaria

CRISTIANA DI CAMPLI, ANTONIO GASBARRINI, ELEONORA NUCERA,
FRANCESCO FRANCESCHI, VERONICA OJETTI, ELENA SANZ TORRE,
DOMENICO SCHIAVINO, PAOLO POLA, GIAMPIERO PATRIARCA,
and GIOVANNI GASBARRINI

Helicobacter pylori, the most important cause of gastritis and peptic ulcer, recently has been associated with several extradigestive diseases. The aim of this study was to assess the prevalence of *Helicobacter pylori* infection and the effects of bacterium eradication in 42 consecutive patients affected by idiopathic chronic urticaria. *Helicobacter pylori* was assessed by [¹³C]urea breath test. Amoxicillin, clarithromycin, and lansoprazole were given to infected patients for seven days. Urticaria and gastrointestinal symptoms were assessed on enrollment and after eradication. Fifty-five percent of patients proved to be infected by *Helicobacter pylori*. Prevalence of gastrointestinal symptoms did not differ between infected and uninfected patients. Eighty-eight percent of infected patients in whom the bacterium was eradicated after therapy showed a total or partial remission of urticaria symptoms. Conversely, symptoms remained unchanged in all uninfected patients. In conclusion, *Helicobacter pylori* affects a high percentage of patients with idiopathic chronic urticaria; however, typical gastrointestinal symptoms do not identify infection status. Bacterium eradication is associated with a remission of urticaria symptoms, suggesting a possible role of *Helicobacter pylori* in the pathogenesis of this skin disorder.

KEY WORDS: *H. pylori*; urea breath test; idiopathic chronic urticaria.

Helicobacter pylori, a gram-negative, microaerophilic spiral bacterium, has been found to infect the gastric mucosa of over half the world's population (1). It has been clearly implicated in the etiology of gastritis and peptic ulcerations (2, 3), and recent studies suggest that *H. pylori* infection could also play a role in some extraintestinal diseases, ranging from rosacea to primary Raynaud phenomenon (4, 5). The heterogeneous clinical features of this infection depend on different possible interactions between *H. pylori* strains and host response (6). In fact, type I bacteria

(which express the vacuolating cytotoxin Vac A and the cytotoxin-associated gene Cag A) were recognized to be more virulent and associated with a more severe inflammatory response (7), and host genetic differences play an important role in the immune response elicited by the *H. pylori* infection.

Chronic urticaria is a skin disorder characterized by recurrent, transitory, itchy wheals, which occur daily or almost daily for at least three months (8). The clinical symptoms are caused by the release of histamine and other vasoactive mediators induced by the binding of an allergen to the specific receptor on mast cells (9, 10). However, in most cases the allergic trigger cannot be determined and the urticaria is considered idiopathic (11). The aim of the present study was to assess the effects of *H. pylori* eradication in infected patients affected by idiopathic chronic

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From the Internal Medicine and Allergology Service, Catholic University, Rome, Italy.

Address for reprint requests: Dr. Antonio Gasbarrini, Istituto di Patologia Medica, Policlinico Gemelli, Largo Gemelli 8, 00168 Rome, Italy.

urticaria and to speculate on the possible pathogenic mechanisms involved in these cases.

MATERIALS AND METHODS

Over a period of six months (October 1996–April 1997), 42 patients (29 females and 13 males; mean age 46 ± 13 years) affected by idiopathic chronic urticaria were included. The cases came from a series of consecutive patients referred to the Allergology Service of Gemelli Hospital. All patients were informed about the study and agreed to participate. The following patients were excluded: (1) those with other current or recent serious diseases; (2) those with a history of atopic diseases and food allergy; (3) those who had received antibiotics or bismuth treatment in the six months before enrollment or K^+ , H^+ -ATPase inhibitors two weeks before enrollment.

On enrollment, each patient completed a standard questionnaire, which included information about demographic factors such as sex, age, educational level, and occupation; and medical history, with particular reference to symptoms of upper gastrointestinal diseases, such as bloating, pyrosis, epigastric pain, belching, halitosis, and nausea.

In order to exclude secondary forms of chronic urticaria, tests for alimentary and inhalatory allergens and for solvents and dyes were performed. In particular, skin tests for common allergens, patch tests, RAST (radioallergosorbent test), and PRIST (paper radioimmunosorbent test) proved negative in all patients. *H. pylori* infection was diagnosed by [^{13}C]urea breath test.

A clinical evaluation of urticaria severity was provided by the same physician on enrollment (T0) by assessing the presence of wheals and erythema. Each variable was graded from 0 (absent) to 3 (severe). A patient self-evaluation of each symptom was also recorded, by rating the severity of wheals, erythema, and daily and nocturnal pruritus on a 4-point scale: 0 (absent), 1 (mild), 2 (moderate), 3 (severe). Furthermore, each patient rated their discomfort from clinical symptoms of urticaria on a 10-cm nongraduated, visual analog scale, ranging from 1 (none) to 10 (very strong).

Triple therapy consisting of amoxicillin (500 mg three times a day), clarithromycin (250 mg three times a day) and lansoprazole (30 mg twice a day) was administered to *H. pylori*-positive patients at the time of diagnosis for seven days. Control of eradication was assessed by [^{13}C]urea breath test six weeks after finishing treatment and the presence of gastrointestinal and urticaria symptoms were assessed one (T1) and three (T2) months after enrollment. Uninfected patients were used as a control group; clinical features of urticaria and gastrointestinal symptoms were evaluated one (T1) and three (T2) months after enrollment.

Results were expressed as mean $\pm$ SEM. Statistically significant differences between groups were assessed by Student's *t* test and ANOVA, when appropriate. $P < 0.05$ was considered to be significant.

RESULTS

H. pylori infection was diagnosed in 23 (15 females and 8 males; mean age 50 ± 11 years) of 42 patients affected by idiopathic chronic urticaria. No significant

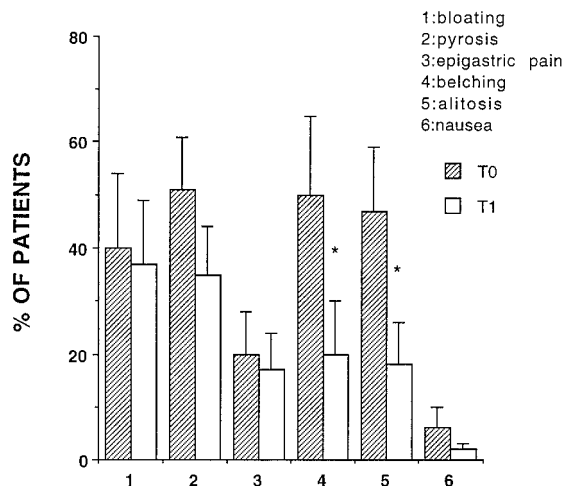


Fig 1. Prevalence of gastrointestinal symptoms in infected patients at the time of enrollment (T0) and one month after eradication (T1). Data are expressed as percentage of patients suffering from each symptom. $P < 0.05$ was considered to be significant.

differences were found as regards sex, age, educational level, and occupation between infected and uninfected patients. Moreover, no significant differences were found either in the discomfort caused by urticaria or in the severity of urticaria symptoms between infected and uninfected patients at the time of enrollment (data not shown). Moreover, the prevalence of gastrointestinal symptoms did not differ between the two groups (data not shown). Therapy for *H. pylori* infection was given to all infected patients, but five patients did not complete the treatment (22% dropout rate). Of the 18 patients who completed the therapy, the bacterium was eradicated in 16 (88%). As regards gastrointestinal symptoms, only belching and halitosis were significantly ($P < 0.05$) reduced after eradication (Figure 1). Considering either the patient self-evaluation or the overall physician assessment, during the follow-up period 13 of 16 patients in whom the bacterium was eradicated showed a total remission of urticaria symptoms and the three remaining subjects showed a partial remission. Amelioration of urticaria symptoms was already evident one month after *H. pylori* eradication (T1) and it was maintained for the three-month follow-up period (Figures 2 and 3). Furthermore, the discomfort caused by clinical symptoms of urticaria was significantly reduced after *H. pylori* eradication in all patients (8 ± 4 at T0 vs 2 ± 3 at T1; $P < 0.05$). Conversely, in the two patients who appeared to be resistant to eradication therapy, both urticaria symptoms and discomfort remained unchanged.

The 19 patients affected by chronic urticaria but not

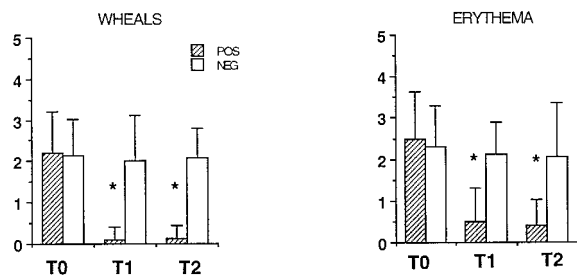


Fig 2. Patient self-evaluation of urticaria symptoms (wheals, erythema, pruritus during the day, pruritus during the night) in infected (POS) patients at the time of enrollment (T0), and one month (T1) and three months (T2) after eradication. Uninfected (NEG) patients were used as a control group; clinical features of urticaria symptoms were evaluated one (T1) and three (T2) months after enrollment (T0). The severity of each symptom was rated on a 4-point scale, ranging from 0 (absent) to 3 (severe). Data are expressed as mean $\pm$ SEM; $P < 0.05$ was considered to be significant.

infected by *H. pylori* (13 females and 6 males; mean age 44 ± 7 years) did not show any significant change either in gastrointestinal symptoms or in urticaria features during the three-month follow-up period

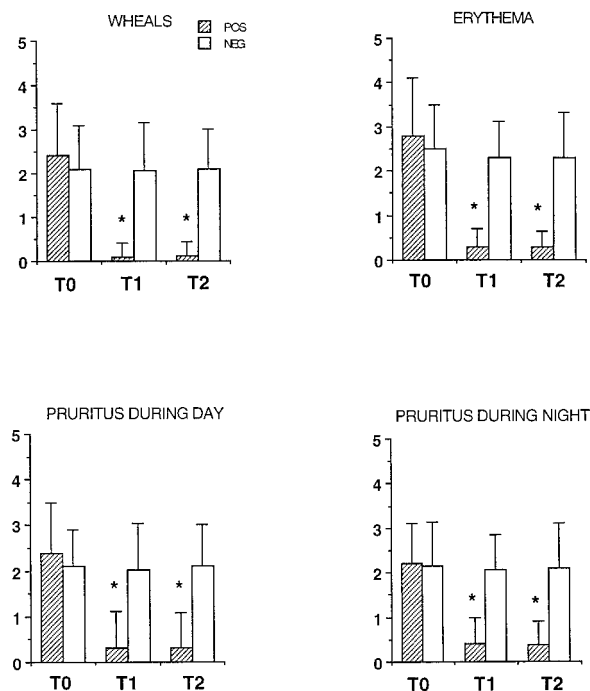


Fig 3. Physician's assessment of urticaria symptoms (wheals and erythema) in infected (POS) patients at the time of enrollment (T0), and one month (T1) and three months (T2) after eradication. Uninfected (NEG) patients were used as a control group; clinical features of urticaria symptoms were evaluated one (T1) and three (T2) months after enrollment (T0). The severity of each symptom was rated on a 4-point scale, ranging from 0 (absent) to 3 (severe). Data are expressed as mean $\pm$ SEM; $P < 0.05$ was considered to be significant.

(Figures 1–3). Moreover, discomfort, as determined by the clinical symptoms of urticaria, did not change significantly either (8 ± 4 at T0 vs 7 ± 5 at T1).

DISCUSSION

The preliminary findings from this study provide substantial evidence that at least some unexplained cases of idiopathic chronic urticaria may be associated with *H. pylori* infection. In fact, eradication of *H. pylori* was accompanied by a total or partial remission of idiopathic chronic urticaria symptoms in all treated patients, whereas the uninfected subjects did not show relevant changes in symptoms. Moreover, there were no differences regarding any of the gastrointestinal symptoms between infected and uninfected patients.

The pathogenic mechanisms that may explain the association between *H. pylori* infection and some cases of idiopathic chronic urticaria are still unknown. However, the increasing evidence of a possible role of *H. pylori* in several extraintestinal diseases (4) suggests that many factors, related to the bacterium and to the host, could play a role in determining the clinical features of *H. pylori* infection (12).

In particular, in subjects affected by idiopathic chronic urticaria, the presence of *H. pylori* gastric infection may result in a stimulation of the immune system to produce a local and systemic inflammatory response for a long period of time (13). In fact, several inflammatory mediators released during the immune response to *H. pylori* infection, such as IL-1, TNF- α , INF- γ , LTC $_4$, and PAF (14) may play a part in the pathogenesis of urticaria lesions (15), at least in producing a nonspecific increase in sensitivity of the cutaneous vasculature to vasopermeability-enhancing agents. It can be also hypothesized that the bacterium may act as an allergic trigger for mast-cell activation, by the action of some *H. pylori* cytotoxins, which could directly induce an influx of Ca $^{2+}$ ions into these cells. It is known, in fact, that several stimuli (such as pharmacological compounds and bacterial toxins) can directly (without the binding of the allergen to the specific IgE) cause mast-cell degranulation, which evokes the clinical symptoms (16). Finally, some authors have reported that two types of functional autoantibodies (against the IgE and the high-affinity IgE receptor), which can produce the histamine release from mast cells, can be identified in the serum of the majority of patients with severe idiopathic chronic urticaria (17, 18). Moreover, other studies have suggested a relationship between idiopathic chronic ur-

ticaria and some cases of autoimmune hypothyroidism (19). Since *H. pylori* has been associated with both disorders (20, 21), it may be implied *H. pylori* infection leads to an autoimmune disease.

In conclusion, although this study was performed in a limited number of patients, it provides evidence that at least some cases of idiopathic chronic urticaria may be associated with *H. pylori* infection and that bacterium eradication may result in a total or partial remission of clinical symptoms. However, further interventional studies are necessary to confirm these results and to test the validity of previous pathogenic hypotheses.

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