

Chronic Urticaria and *Helicobacter pylori*

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Chronic urticaria can result from multiple causes. A number of factors have been identified that can appear to be important in the pathogenesis of individual cases, including intolerance to food, drugs, some internal diseases and some infections. Recently a possible relationship between chronic urticaria and *Helicobacter pylori* has been suggested. One hundred and twenty-five patients were investigated for *Helicobacter pylori* infection by means of ELISA assay and 13C urea-breath tests. When the two tests were positive, gastric biopsy was performed after informed consent. Patients with *Helicobacter pylori* infection were randomly assigned to receive triple therapy for the eradication of bacterium for one week, or no treatment. As controls, 25 patients with chronic urticaria and with negative results on ELISA and urea-breath tests were treated with the same triple therapy course. Forty-six unrelated blood donors of both sexes were examined for the presence of anti-*Helicobacter pylori* antibodies in the normal population. Seventy-eight patients had circulating specific IgG antibodies against the bacterium and positive urea-breath tests. Among these patients, 31 received eradication therapy, 34 were enrolled in the control group, and 13 patients neglected the study.

Three patients in the eradication therapy group showed complete remission of urticaria after 12 months of follow-up as compared with 1 patient in the control group. Twenty blood donors out of 46 were IgG anti-*Helicobacter pylori* positive.

In conclusion, our data show that the prevalence of *Helicobacter pylori* infection is high in chronic urticaria patients, but eradication of the bacterium does not appear to influence the skin disorders nor the symptoms. **Key words:** *Helicobacter pylori*; chronic urticaria; ELISA; urea breath test; short-term triple therapy.

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Chronic urticaria (CU) can result from multiple causes and probably does not have a single aetiology. A number of factors have been identified that appear to be important in the pathogenesis of individual cases, including intolerance of certain food additives, non-steroidal anti-inflammatory drugs including aspirin, some internal diseases, and some infections (1, 2). During the last few years, some authors have reported their experience about cases of chronic urticaria related to the presence of *Helicobacter pylori* (HP) infection (3, 4).

HP is a microaerophilic Gram-negative bacterium, periodic infection with which is associated with reduced gastric acid secretion, whereas chronic infection with HP is associated with increased secretion of acid and pepsin (5). The recent and interesting data (3) previously mentioned prompted us to evaluate the prevalence of HP infection in patients with CU and the effects of eradication therapy on the outcome of the skin disease.

MATERIAL AND METHODS

One hundred and twenty-five unselected patients (45 men and 80 women, age range 24–61 years) with chronic urticaria seen consecutively from June 1993 to November 1996 in our two departments (Bergamo and Milan) were included in the study.

Patients referred urticarial lesions and sometimes angioedema almost daily for more than 3 months. Each patient had a complete history taken and underwent the following tests: complete blood count, total eosinophil count sedimentation rate, complete urine examination, liver function test, serum tests for HCV and HBV infections, cryoglobulins, rheumatoid factor, anti-nuclear factor, C3, C4, and C1-inhibitor, T3 free, T4 free, TSH, stool examination for parasites, and total IgE (PRIST).

The following placebo-controlled tests were done when indicated by the patient's history: prick tests with a panel of common inhalants and food allergens (animal dander, pollens, house dust mites, milk, egg, nut, tomato, codfish, wheat, peach, banana), investigations for focus of infection in various locations (teeth, upper respiratory and urogenital tracts) and an oral provocation challenge test with dyes and food additives. Patients suffering from physical urticaria were excluded by questionnaire and by the specific test on physical examination.

For HP infection, the patients were examined with a commercially available ELISA test for specific IgG antibodies against the bacterium and by the urea breath test. If both tests were positive, gastroscopy with mucosal biopsy was proposed to verify the presence of HP. Each patient was informed, and after consent was given, the examination was performed.

Patients positive for HP infection were randomly assigned to receive triple therapy for the eradication of HP with omeprazole 20 mg twice daily, clarithromycin 250 mg twice daily and metronidazole 250 mg twice daily for one week, or no treatment. Eradication of HP infection was confirmed by 13C urea-breath test 8 weeks after the end of therapy, and clinical assessment of CU was done every second month for one year. As control, 25 patients with CU and with ELISA and urea-breath test negative results were treated with the same triple therapy course.

Forty-six unrelated normal blood donors of both sexes with mean ages of 38.7 ± 16.6 years were examined for the presence of anti-HP antibodies in the normal population.

RESULTS

Among the 125 patients suffering from CU and investigated for HP infection, 78/125 (62%) had circulating specific IgG antibodies against the bacterium and positive urea-breath tests. The prevalence of HP infection was similar in both sexes (61% in men and 62% in women); no differences between HP positive and negative patients were found regarding age and presence of dyspeptic symptoms. Twenty-three patients out of 78 with HP-positive results accepted gastroscopy and biopsy of the gastric mucosa; all these patients tested positive for HP presence during histologic examinations. Among the 78 HP-positive patients, 31 received eradication therapy and 34 were enrolled in the control group and were only observed on follow-up. Thirteen patients out of 78 with CU and HP-positive results withdrew from the study. In the treated group, eradication of the bacterium was achieved in all patients but 2. At 2 and 4 months follow-up, 6 patients in the eradication group

showed remission of CU as compared with 3 patients in the group with no treatment. At 6 and 8 months of follow-up, 3 patients (10%) in the eradication therapy group showed persistent remission of urticaria as compared with one patient in the control group; after 12 months of follow-up, the situation was the same. Among the 25 CU patients without HP infection treated with triple therapy, one showed remission of skin symptoms at 4, 8 and 12 months follow-up.

The HP serology studied in 46 unrelated blood donors showed the following results: 20 subjects (43%) were IgG anti-HP-positive, and the seropositivity increased with age (from 20% in subjects aged 20–30 years to 67% in subjects aged 50–60 years). Finally, the generic laboratory tests and investigations revealed no significant evidence of another underlying disease, and no intolerance to food or food additives.

DISCUSSION

The association between chronic urticaria and HP is poorly documented in the literature. Rebora et al. (3), in their experience of 7 patients, found anti-HP antibodies in 4; Tebb et al. (4) presented a study of 25 patients with CU where HP infection was diagnosed in 17; eradication of the bacterium in these 17 subjects was accompanied by clinical remission in 14.

We investigated 125 patients with CU for HP infection using an ELISA assay for specific antibodies and with a urea-breath test, and we observed in 78 of them (62%) the presence of HP infection. The random distribution of these patients to eradication triple therapy of HP or to no treatment showed that 3 patients (10%) in the treatment group had a complete remission of skin symptoms one year after the end of therapy, compared to one patient out of 34 enrolled in the group with no treatment. The findings obtained from this study seem to show that the HP infection can affect a high percentage of patients (62%) with CU, but eradication of the bacterium does not appear to influence the skin condition nor the symptoms.

HP eradication seems to be difficult to achieve. It requires the concurrent administration of two or more drugs (6); it is suggested that the short-term triple therapy combination used in this study can eradicate the HP infection in 90–95% of patients (7).

The study of the distribution of anti-HP antibodies in the general population revealed that seropositivity was detected in the 43% of sample studied, and that there was no difference between sexes. These data are consistent with those obtained in a recent population study of HP infection in a European Mediterranean area, San Marino (8), where anti-HP antibodies were present in 51% of subjects investigated.

The pathogenetic mechanism that may exist between chronic urticaria and HP infection remains unknown, but it is possible to speculate about it. Chronic infection increases secretion of gastric acid and pepsin, and the enhanced acid load could induce gastric metaplasia and active inflammation. One of the hallmarks of inflammation is the progressive recruitment of inflammatory cells with accumulation of neutrophils and subsequent increase of eosinophils (mainly) and lymphocytes. The participation of this complex network of inflammatory cells and the subsequent mediator release could support the occurrence of late-phase persistent inflammatory changes. Although the contribution of inflammatory cells to urticarial lesions is not well understood, lymphocytes and neutrophils are known to release a family of histamine-releasing factors

that induce mast cell degranulation (9). Similarly, eosinophils store several mediators, including major basic protein, in their granules, which, when released, may cause mast cell degranulation (10).

The possibility that mast cell and basophil mediator release can be induced by several triggers other than IgE (anaphylotoxins C3a and C5a, I1s, etc.) is now largely proven. This mechanism might explain how trigger factors other than allergens (such as food, drugs, and other chemical substances) might induce pseudo-allergic reactions which are similar, at a clinical level, to typical IgE-mediated immediate hypersensitivity reactions, and this evidence could be supported by the modified morphology of the gastro-intestinal tissue.

It is known that the gastrointestinal tract is richly populated with lymphoid tissue and a large variety of immune cells (B- and T-lymphocytes, plasma cells, macrophages, mast cells, eosinophils and basophils) capable of initiating and effecting a wide variety of immunologic reactions. This tissue is the GALT (gut-associated-lymphoid tissue) that belongs to the MALT (mucosal-associated-lymphoid tissue), and the reactions related to it have consequences not only for the gastrointestinal tract itself, but for the body in general. On the inner surface of the gastrointestinal tract, our organism comes in intimate contact with bacteria, parasites, enzymes, toxins and various dietary substances and their breakdown products. All these substances and agents, including HP itself and its toxin may affect GALT homeostasis and may activate an immune response (11).

On the other hand, we must remember that an HP toxin release and a subsequent possible complement activation could occur. During the complement activation process, there is the generation of the anaphylotoxins C3a and C5a; the interaction of these complement fragments with specific receptors on mast cells and basophils causes release of histamine. In conclusion, the findings observed in a large number of patients with chronic urticaria seem partially to confirm previous limited reports about the possible relationship between HP infection and the skin disease, but eradication of HP does not appear to influence the skin condition nor the symptoms.

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