

Relationship between *Helicobacter pylori* and idiopathic chronic urticaria: effectiveness of *Helicobacter pylori* eradication

Majid Rostami Mogaddam¹, Abbas Yazdanbod², Nastaran Safavi Ardabili³, Nasrollah Maleki⁴, Sonia Isazadeh¹

¹Department of Dermatology, Imam Khomeini Hospital, Ardabil University of Medical Sciences, Ardabil, Iran

²Department of Gastroenterology, Imam Khomeini Hospital, Ardabil University of Medical Sciences, Ardabil, Iran

³Department of Midwifery, Ardabil Branch, Islamic Azad University, Ardabil, Iran

⁴Department of Internal Medicine, Imam Khomeini Hospital, Ardabil University of Medical Sciences, Ardabil, Iran

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Abstract

Introduction: Chronic urticaria (CU) is defined as the presence of urticaria on most days of the week for a period of 6 weeks or longer. Some studies have reported an association between CU and *Helicobacter pylori* (*H. pylori*) infection.

Aim: To determine the prevalence of *H. pylori* infection using the stool antigen test in patients with idiopathic CU and to investigate the infected patients with CU following eradication of *H. pylori*.

Material and methods: One hundred patients with idiopathic CU and 100 healthy controls were referred to our clinic between May 2012 and June 2013 and were tested for *H. pylori* antigen. The patients infected with *H. pylori* received quadruple therapy for 2 weeks. To assess eradication efficacy, a repeated *H. pylori* stool antigen test was performed in each patient 6 weeks after the end of anti-*H. pylori* therapy. The effectiveness of eradication therapy on CU was assessed 3 months after treatment.

Results: Thirty-six percent patients with idiopathic CU were infected with *H. pylori* while 23% of the controls were infected. Response to eradication therapy was evident in 33 (91.67%) patients in whom *H. pylori* was eradicated while 3 (8.33%) patients showed no response despite eradication of *H. pylori*. Clinical follow-up of 33 successfully treated patients 3 months later revealed complete remission of urticaria in 54.5%, partial remission in 18.2%, and no improvement in 27.3%.

Conclusions: The results of our study suggest that *H. pylori* infection should be included in diagnostic workup of patients with no response to habitual treatment for CU or symptomatic gastrointestinal patients. For the diagnosis of *H. pylori* infection, one should consider the costs and accessibility of the population to the HpSA[®] stool antigen test and Urea breath test (UBT).

Key words: chronic urticaria, *Helicobacter pylori*, eradication.

Introduction

Chronic urticaria (CU) is defined as the occurrence of daily, or almost daily, wheals and itching for at least 6 weeks. It is a common and potentially debilitating skin condition that affects up to 1% of the general population with variable duration, typically several months, but occasionally decades [1]. Chronic idiopathic urticaria (CIU), defined as the occurrence of CU, with no obvious cause, constituting up to 70% of cases [2, 3].

Both children and adults can develop CU, although it is more common in adults. Women are affected twice as often as men, and the condition typically begins in the third to fifth decade of life [4, 5]. Although not the sole cause of symptoms, certain factors aggravate CU in a substantial subset of patients. These include physical factors, nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, stress, and food allergy.

Address for correspondence: Dr. Nasrollah Maleki, Department of Internal Medicine, Imam Khomeini Hospital, Ardabil University of Medical Sciences, 4513432453 Ardabil, Iran, phone: +98 9163057715, e-mail: malekinasrollah@yahoo.com

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Chronic urticaria is associated with various autoimmune disorders [4]. There is a possible association with malignancies, although data are conflicting [6]. None of the theories of pathogenesis of CU has been fully established [7]. The best-developed hypotheses include the autoimmune theory, theories involving histamine-releasing factors, and the cellular defects theory. Attempts have been made to associate some common chronic infections with CU, including *Helicobacter pylori* [8, 9], hepatitis A [10], and hepatitis C [11].

Chronic *H. pylori* gastritis affects two-thirds of the world's population and is one of the most common chronic inflammatory disorders of humans. The major clinical associations with chronic *H. pylori* gastritis are peptic ulcer disease and, less commonly, gastric cancer and lymphoma. Recent evidence suggests that *H. pylori* infections play a role in the pathogenesis of a variety of skin diseases [12]. It is known that CU occasionally develops with *H. pylori* infection, but the association between urticaria and *H. pylori* remains unknown [13].

Aim

The aim of this study is to determine the prevalence of *H. pylori* infection using the stool antigen test in patients with CU and to investigate the infected patients of CU following eradication of *H. pylori*.

Material and methods

Patients and controls

This study was approved by the Ethics Committee of the Ardabil University of Medical Sciences. This was a prospective cross-sectional study. Patients presenting with CU to the dermatology out-patient clinic of Imam Khomeini Hospital in Ardabil, Iran, between May 2012 and June 2013 were recruited for the study. A total of 100 patients with idiopathic CU and 100 healthy controls were included. The two groups were matched for age and sex. Physical examination and laboratory tests (complete blood cell count, renal and liver function, fasting blood glucose, serum creatinine, erythrocyte sedimentation rate, antinuclear antibody, complement assays, and thyroid function test) were

carried out at baseline and were normal to exclude other etiologies than *H. pylori*. Patients who met the following criteria were enrolled into this study: (1) urticaria duration of at least 6 weeks; (2) no cause of urticaria found despite extensive laboratory tests; (3) existence of gastrointestinal symptoms in the medical history; and (4) consent to participate in the study. Criteria for exclusion included: (1) use of antibiotics, bismuth, or proton-pump inhibitors within the prior 4 weeks; (2) patients with previous gastric surgery; and (3) the coexistence of serious concomitant illness (e.g. decompensated liver cirrhosis or uremia).

The *H. pylori* stool antigen test was performed in all study subjects. Prior to sampling, the questionnaire, including medical history and demographic data, was completed for each patient. All studied patients signed an informed consent form and declared their willingness to allow the application of their anonymous data for research purposes. Table 1 shows the characteristics of the CU group and control group.

The patients infected with *H. pylori* received quadruple therapy with omeprazole (20 mg twice daily), amoxicillin (1 g twice daily), bismuth subcitrate (240 mg twice daily), and clarithromycin (500 mg twice daily) for 2 weeks. All patients were followed up during the study duration of 3 months. To assess eradication efficacy, a repeated *H. pylori* stool antigen test was performed in each patient 6 weeks after the end of anti-*H. pylori* therapy. The effectiveness of eradication therapy on CU was assessed 3 months after treatment, using a three-point rating scale, that is, complete remission, partial remission (50% or more), or no improvement.

Helicobacter pylori stool antigen test

A fresh stool sample was collected from each patient and stored at -20°C until analyzed. The *H. pylori* stool antigen test (GA GENERIC ASSAYS GmbH, Germany) was performed according to the manufacturer's recommendation. According to the manufacturer's instructions (spectrophotometer, Avernast, stat fax 3200, USA), the cut-off value was obtained by the mean OD of negative control at 450 nm, plus 0.1. $\text{OD} \leq \text{cut-off}$ was defined negative, $\text{OD} > \text{cut-off}$ was considered positive.

Table 1. Characteristics of chronic urticaria (CU) group and control group

| Characteristics | Patients with CU (N = 100) | Controls (N = 100) | Value of p |
|---------------------------------|----------------------------|--------------------|------------|
| Age [year] | 37.64 \pm 16.04 | 37.55 \pm 16.26 | 0.943 |
| Gender (male/female) | 58/42 | 58/42 | 1.000 |
| Place of residence (rural/city) | 44/56 | 39/61 | 0.840 |
| Education duration [year] | 6.8 \pm 1.2 | 7.1 \pm 0.3 | 0.950 |
| BMI [kg/m ²] | 70.2 \pm 12.2 | 69.7 \pm 11.3 | 0.850 |
| CU disease duration [month] | 15.34 \pm 10.73 | – | – |

BMI – body mass index.

Statistical analysis

Diagnostic methods were compared by χ^2 and Student *t*-test statistical analysis, and *p* value of < 0.05 was considered statistically significant. The statistical analysis was performed using analysis of variance and SPSS software (Version 19, SPSS Inc, United States).

Results

Two hundred patients were enrolled in the study (100 cases and 100 controls). In both groups, 58% were male and 42% were female. The mean age in the patients group was 37.64 ± 16.04 years and in the control group it was 37.55 ± 16.26 years. Other findings in the patients group were asthma (12.8%), allergic rhinitis (14.3%), and angioedema (47.8%). Based on the clinical characteristics of CU patients, the duration of the last CU episode was relatively long, between 5 months and 6 years (median 15.34 months). All patients had received medications before coming to our clinic and most of them (94.13%) had combination therapy.

Thirty-six percent patients with CU were infected with *H. pylori* while 23% of the controls were infected. There was statistically a significant difference (*p* = 0.044) between the prevalence of *H. pylori* in patients with CU and controls. The infected patients with CU achieved quadruple therapy with omeprazole, amoxicillin, bismuth subcitrate, and clarithromycin for 14 days. Response to eradication of *H. pylori* was evident in 33 (91.67%) patients in whom *H. pylori* was eradicated while 3 (8.33%) patients showed no response despite eradication of *H. pylori*. Clinical follow-up of 33 successfully treated patients 3 months later revealed complete remission of urticaria in 54.5% (18/33), partial remission in 18.2% (6/33), and no improvement in 27.3% (9/33). In other words, 72.7% (24/33) successfully treated patients showed remission of urticaria, while 27.3% (9/33) successfully treated patients showed no response.

Discussion

Helicobacter pylori is a bacterium that is found in the stomach and is responsible for most cases of peptic ulcer and is one of the most common bacterial infections in humans [14]. There are several tests available to detect the presence of *H. pylori* in the stomach. Among non-invasive diagnostic tests, *H. pylori* stool antigen test (HpSAT) and urea breath test (UBT) have higher accuracy than serological or urinary antibody-based tests. The American Gastroenterological Association recommends both HpSAT and UBT for the diagnosis of *H. pylori* infection in patients with dyspepsia [15]. The HpSAT has high sensitivity and specificity and is used for diagnosis as well as monitoring after treatment [16].

The importance of biofilm in the pathogenesis of *H. pylori* infection is not fully understood. Many research-

ers suggest that it may be responsible for the failure of *H. pylori* eradication and contribute to the survival of microorganisms in the focal infection, leading to reinfection [17]. Although Sonic hedgehog (Shh) signaling pathway plays a principal role in gastric carcinogenesis, its role in *H. pylori*-associated gastritis is unclear. The results of some studies support the hypothesis of the involvement of Shh signaling pathway in *H. pylori*-associated gastritis [18].

Helicobacter pylori has been implicated in a variety of diseases that are not related to the gastrointestinal tract. The skin is an example and several studies have suggested an association with the following conditions [19, 20]: CU, rosacea, psoriasis, Sjögren syndrome, Henoch-Schönlein purpura, alopecia areata, Sweet disease, systemic sclerosis, atopic dermatitis, Behçet's disease, generalized pruritus (itch), nodular prurigo, immune thrombocytopenic purpura, lichen planus, and aphthous ulceration. A possible role for *H. pylori* in the pathogenesis of gastroesophageal reflux disease (GERD) has also been suggested in a growing number of studies. The association between *H. pylori* infection and functional dyspepsia (FD) is unclear. Whether patients with FD should receive *H. pylori* eradication therapy remains controversial [21].

Several studies have found a link between *H. pylori* infection and CU. It is thought that infection with *H. pylori* increases the permeability of the stomach lining and thus increases the exposure to allergens (substances that causes an allergy) in the gastro-intestinal tract. Also, the immune response to *H. pylori* produces antibodies that may encourage release of histamine in the skin [22]. IgE-containing cells in gastric and duodenal mucosa seem to be the culprits, although there is limited evidence for HP-specific IgE. Thus, the possibility that patients with urticaria develop specific IgE against *H. pylori* is an attractive pathogenic explanation that unfortunately has not been confirmed yet [19].

The immunomodulatory role of *H. pylori* infection in CU is a subject of intensive debate. This immunomodulation is not only dependent on the virulence of *H. pylori* but also on host and environmental factors. An alternative possibility is that immunological stimulation by chronic infection may produce, through mediator release, a non-specific increase in sensitivity of the cutaneous vasculature to agents that enhance vascular permeability [19]. Furthermore, IgG and IgA antibodies to 19-kDa *H. pylori*-associated lipoprotein were found to play a role in the pathogenesis of CU [23].

A number of studies in several countries showed the high prevalence of *H. pylori* infection in CU patients, followed by clinical remission of CU after *H. pylori* eradication therapy. In the first one of these studies, back in 1994, Kolibasova *et al.* [24] assessed 21 patients with chronic urticaria and *H. pylori* infection. Eradication therapy against the bacterium led to remission of urticaria in 95% of the cases. Later on, Bohmeyer *et al.* [25] in 1996,

Table 2. Association between chronic urticaria (CU) and *H. pylori* infection in the literature

| Reference | Country | Year | Total number of patients with CU | Number of <i>H. pylori</i> positive patients (%) | Urticaria remission after eradication (%) |
|-----------------------------------|---------|------|----------------------------------|--|---|
| Bohmeyer <i>et al.</i> [25] | Germany | 1996 | 10 | 8 (80) | 8/8 (100) |
| Tebbe <i>et al.</i> [34] | Germany | 1996 | 25 | 17 (68) | 14/17 (82.3) |
| Valsecchi <i>et al.</i> [45] | Italy | 1998 | 125 | 31 (62) | 3/29 (10) |
| Di Campli <i>et al.</i> [9] | Italy | 1998 | 42 | 18 (42.8) | 13/16 (81.2) |
| Ozkaya-Bayazit <i>et al.</i> [35] | Turkey | 1998 | 35 | 23 (65.7) | 5/17 (29.4) |
| Bonamigo <i>et al.</i> [36] | Brazil | 1999 | 18 | 18 (100) | 10/12 (83.3) |
| Daudén <i>et al.</i> [37] | Spain | 2000 | 25 | 15 (60) | 8/14 (57) |
| Erel <i>et al.</i> [44] | Turkey | 2000 | 38 | 29 (76) | 1/25 (4) |
| Sakurane <i>et al.</i> [38] | Japan | 2002 | 50 | Not stated | Not stated |
| Fukuda <i>et al.</i> [39] | Japan | 2004 | 50 | 19 (38) | 17/17 (100) |
| Magen <i>et al.</i> [40] | Israel | 2007 | 78 | 45 (57.7) | Not stated |
| Yadav <i>et al.</i> [41] | India | 2008 | 68 | 48 (70.58) | 39/48 (81.2) |
| Akashi <i>et al.</i> [42] | Japan | 2011 | 82 | 25 (30.5) | Not stated |
| Chiu <i>et al.</i> [43] | Taiwan | 2013 | 14 | 11 (78.6) | 8/11 (72.7) |
| This study | Iran | 2014 | 100 | 36 (36) | 24/33 (72.7) |

carried out endoscopic assessment in 10 patients with CU, finding *H. pylori* in the gastric mucosa in 8 of them; they reported that the skin lesions disappeared within a few days of treatment with amoxicillin and omeprazole. Table 2 shows a possible association between CU and *H. pylori* infection in the literature.

In the present study, we found that the prevalence rate of *H. pylori* infection is 36% in our CU patients. Twenty-four (72.7%) successfully treated patients showed remission of urticaria, while 9 (27.3%) successfully treated patients showed no response. Wustlich *et al.* [26] studied 30 patients with CU and *H. pylori* infection, who were given eradication therapy with amoxicillin and omeprazole; the success or otherwise of the eradication therapy was assessed using a breath test (the eradication ratio was 80%). After 6 months' follow-up they observed improvement or remission of the urticaria in 8 patients (26.7%). However, this study had no control group, and the results are compared to a published 6% spontaneous remission rate of urticaria. The results of this study did not support the preliminary data of previous studies.

Conflicting reports have been published. Some suggest that *H. pylori* eradication in patients with CU leads to an improvement in the symptoms of CU, while others showed no improvement (Table 2). Hellmig *et al.* [27] concluded that there is no evidence that eradication of *H. pylori* improves the outcome in patients with CU. The high rate of spontaneous remission and the coexistence of multiple foci will always obscure the evaluation of any specific antimicrobial therapy.

In 2012, Kołacińska-Flont *et al.* [28] have compared the anti-*H. pylori* IgG titer in 62 patients with CIU and

55 control subjects and evaluated the effect of *H. pylori* eradication on urticaria. They concluded that the anti-*H. pylori* IgG titer was similar in patients with CIU and controls. *Helicobacter pylori* eradication had no effect on urticaria in anti-*H. pylori* IgG positive CIU patients with gastric complaints. In 2014, Yoshimasu *et al.* [13] studied the effect of eradication therapy for urticaria with high titers of anti-*H. pylori* IgG antibody. They concluded that, regardless of it being acute or chronic urticaria, the high titer of anti-*H. pylori*, IgG antibody can be an indicator for undergoing upper endoscopy, and eradication therapy would be strongly recommended.

In CU there is a lot of evidence for different infections, but randomized controlled trials are missing. The prevalence of infections is not increased but in susceptible patients the immune response may lead to the development of CU. Interestingly, there is evidence for an infection-associated auto reactive response at least in the subgroup with a positive autologous serum skin test. A variety of mechanisms have been invoked to explain these observations, including molecular mimicry. Some bacterial infections such as *Streptococcus*, *Mycoplasma pneumoniae*, *Borrelia* can be also found in association with CU [10]. The therapeutic response observed following the administration of amoxicillin and clarithromycin (two broad-spectrum antibiotics) may also be due to the eradication of other bacteria related to CU. In order to improve the healing effectiveness and to decrease the risk of adverse effects, not only appropriate drug selection but also optimal dosage and duration of treatment are essential [29].

As recent studies have demonstrated, IgG autoantibodies against IgE and/or FcεR1α can be found in the sera of one-third of patients with idiopathic CU, and it is postulated that infection with *H. pylori* may induce production of pathogenic antibodies possibly by molecular mimicry [30]. A growing body of evidence suggests that 30–50% of CU results from an autoimmune process involving functional histamine-releasing anti-FcεR1α autoantibodies or less commonly, anti-IgE-autoantibodies [31]. Once this occurs, the production of antibodies might continue even after the eradication of *H. pylori* infection, explaining the lack of clinical improvement after eradication seen in some studies [19].

To summarize, clinical trials including large numbers of patients are needed to establish a possible relationship between gastrointestinal findings and CU. To cure at least some patients from quality-of-life reducing CU, it seems worthwhile to eradicate *H. pylori* in all patients with CU and *H. pylori* infection. A positive effect is proposed for the eradication of *H. pylori* [19, 32, 33].

Conclusions

Helicobacter pylori may have a role in some patients with idiopathic CU. The results of our study suggest that *H. pylori* infection should be included in diagnostic work-up of patients with no response to habitual treatment for CU or symptomatic gastrointestinal patients. For the diagnosis of *H. pylori* infection one should consider the costs and accessibility of the population to the HpSA® stool antigen test and urea breath test (UBT).

Conflict of interest

The authors declare no conflict of interest.

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