

Report

Lack of correlation between *Helicobacter pylori* infection and autologous serum skin test in chronic idiopathic urticaria

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Abstract

Background There are controversial reports about the direct role of *Helicobacter pylori* infection in chronic idiopathic urticaria. The indirect role of *H. pylori* infection in the induction of pathogenetic antibodies is not fully elucidated either. This study aims to reveal the association of *H. pylori* infection with autologous serum skin test positivity in chronic idiopathic urticaria (CIU) patients.

Methods A total of 47 patients (35 women, 12 men, age range 17–65 years) diagnosed as CIU were included in the study. Autologous serum skin test was performed on all patients. The patients were examined with a commercially available ELISA test for *H. pylori*-specific antibodies. Gastroscopy with mucosal biopsy and rapid urease tests were proposed to verify the presence of *H. pylori* infection.

Results *Helicobacter pylori* infection was detected in 33 of the 47 patients (70%). No significant relation was found between the autologous serum skin test positivity and the serological and histopathological presence of *H. pylori* infection.

Conclusion The results of our study suggest that chronic *H. pylori* infection does not appear to have a role in the induction of autoantibodies in CIU.

Introduction

Chronic idiopathic urticaria (CIU) is defined as widespread short-lived (< 24 h) wheals occurring daily or almost daily for at least 6 weeks, where a predominant physical cause has been excluded.¹ It is a common and extremely distressing disorder, occurring in 0.1 % of the population and causing severe occupational, social, personal and domestic disability.^{2,3} The pathogenesis of CIU has not yet been fully elucidated and a triggering factor could be indicated in only a minority of cases. Food additives, chronic infections and infestations have been proposed as etiological factors for mast cell degranulation.² The most recently cited chronic infection is *Helicobacter pylori*. However, there are controversial comments about the direct role of *H. pylori* in the etiology of CIU.^{4,9} As recent studies have demonstrated IgG autoantibodies against IgE and/or FcεR1α in the serum of one-third of their patients with CIU, it is postulated that infection with *H. pylori* may induce development of pathogenetic antibodies possibly by molecular mimicry, but available clinical data on the association of *H. pylori* infection with autologous serum skin test positivity are limited.^{2,10}

Intradermal injection of autologous serum, the autologous serum skin test (ASST) as defined by Sabroe *et al.*,¹¹ is a reasonably sensitive and specific test for basophil histamine

release in some patients with CIU. Our study was performed to determine the association of *H. pylori* infection with autoimmune-based CIU.

Materials and Methods

A total of 47 patients (35 women, 12 men, age range 17–65 years) diagnosed as CIU after extensive investigations were included in the study. Each patient had a complete history taken, especially for immunologic and autoimmune disorders, and underwent the following tests: complete blood count, total eosinophil count, erythrocyte sedimentation rate, complete urine examination, liver function test, hepatitis screen, cryoglobulins, rheumatoid factor, antistreptolysin-o, immunoglobulins, complement, antinuclear, antineutrophil cytoplasmic antibodies, antithyroid microsomal antibody, thyroid function test, stool examination for parasites and total IgE level. The following test were performed when indicated by the patient's history: prick tests with a panel of common inhalants and food allergens, investigations for focus of infection in various locations, and oral provocation challenge tests with dyes and food additives. In all patients, physical urticaria was excluded by history and/or diagnostic tests.

For *H. pylori* infection, the patients were examined with a commercially available ELISA test for specific IgG and IgM antibodies. If antibody positivity was detected, gastroscopy with

mucosal biopsy and a rapid urease test were proposed to verify the presence of *H. pylori* infection. Those patients who gave consent for the endoscopic examination were included in the study.

The skin test technique, as previously defined by Sabroe *et al.*,¹¹ was performed as follows: Venous blood was taken into sterile glass tubes without clotting accelerator and allowed to clot at room temperature for 30 min. Serum was separated by centrifugation at 500 g for 15 min. Fifty-microliter aliquots of autologous serum, 0.9% sterile saline (negative control) and histamine (10 µg/ml, positive control) were injected into the dermis of the volar aspect of both forearms. Wheal and flare responses were evaluated at 30 min, and previously determined parameters of the ASST with optimal sensitivity and specificity were used to define test positivity.¹¹ The ASST response was taken to be positive when the serum-induced wheal had a diameter at least 1.5 mm greater than the saline-induced wheal. The ASST test was performed by two dermatologists to avoid interpersonal variation in performing and interpreting the test. In all subjects, antihistamines were withdrawn at least 1 week before the skin tests. No subject was taking immunosuppressant therapy for at least 3 months before testing.

The study was approved by the Ethics Committee of the University Hospital of Uludag.

Results

The mean duration of CIU was 2.66 years (SD: 1.687). *Helicobacter pylori* infection was detected in 33 of the 47 patients (70%). *H. pylori*-specific IgG positivity was also present in 30 of these patients, revealing the existence of a chronic infection. Only three of the patients did not have *H. pylori*-specific IgG antibodies but had *H. pylori*-specific IgM antibodies, suggesting the presence of the first attack of the infection. The histopathological examination revealed *H. pylori* infection and the rapid urease test was positive in these three patients. The ASST was found to be positive in two of them. The results of the ASST and other parameters associated with *H. pylori* infection are summarized in Table 1.

Fisher's exact test was used for the comparison of the results of the parameters among themselves. The relation

between the ASST results and the presence of histopathologic evidence for *H. pylori* infection as well as *H. pylori*-specific IgG antibodies was found to be statistically insignificant ($P = 0.1946$).

Discussion

The direct role of *H. pylori* infection of the upper gastrointestinal tract in the etiology of CIU is still controversial. While several authors demonstrated that *H. pylori* eradication therapy was associated with the remission of chronic urticaria, suggesting a possible role in etiology, others produced the opposite result.^{4,9} Recent controlled studies have not revealed any evidence of benefit from eradication of *H. pylori* either.^{7,12} However, the lack of correlation between *H. pylori* eradication and remission of chronic urticaria led to the postulation of a more indirect role.

As mentioned previously, there is now growing evidence that 30–50% of CIU results from an autoimmune process involving functional histamine-releasing anti-FcεRIα autoantibodies or less commonly, anti-IgE-autoantibodies.¹² As patients with autoimmune antibodies have no distinctive diagnostic clinical features, current clinical diagnosis depends on autologous serum skin testing. A positive test is suggestive but not diagnostic of an autoimmune basis.³ Although Western blot analysis or an enzyme-linked immunosorbent assay (ELISA) test was developed to detect autoantibodies, these tests do not distinguish functional histamine-releasing antibodies from nonfunctional antibodies.^{13,14} These time-consuming tests are only performed in a few specialist laboratories and are not available in our department, and neither in the majority of clinics. It has already been reported that the ASST, with a positive test being defined as one with a serum-induced wheal which is both red and has a diameter of 1.5 mm greater than the saline-induced response at 30 min, is a reasonably predictive clinical test to reveal functional circulating antibodies with a sensitivity of 65–71% and specificity of 78–81%.¹¹ Thus, we relied on the ASST, the only available and practical test, to demonstrate those patients with autoantibodies.

It is postulated that *H. pylori* may induce development of pathogenic autoantibodies by molecular mimicry.² Once this occurs, the production of antibodies might continue even after the eradication of *H. pylori* infection, explaining the lack of clinical improvement in previous studies.^{6–8,10} Appelmek *et al.*¹⁰ first demonstrated the molecular mimicry between *H. pylori* and lipopolysaccharide (LPS) and anti-Lewis antibodies in autoimmune type-B gastritis. Further evidence was provided by the highly positive ASST results in chronic urticaria patients with *H. pylori* IgG antibody.¹⁶

In our study, we compared the results of ASST with *H. pylori* IgG antibodies and gastroscopy findings, including histopathologic examination and rapid urease test. The sensitivity and specificity of *H. pylori*-specific IgG antibody is

Table 1 Results of an autologous serum skin test in chronic idiopathic urticaria patients with *Helicobacter pylori* infection

	Histopathologic evidence of <i>H. pylori</i> infection (n)*	
	+	–
ASST (+)	22	6
ASST (–)	11	8

* $P = 0.1946$ by Fisher's exact test, 95% CI: 0.7395–9.616. ASST = autologous serum skin test.

determined to be 95.8 and 95.5%, respectively. As a result of their limited diagnostic value, IgM antibodies were not included for statistical comparison.¹⁷ All of the patients were asked to undergo endoscopy, which has a specificity and sensitivity of nearly 100%, to evaluate the presence of an infection.

The prevalence of *H. pylori* infection in the Turkish population ranges from 70 to 90%.¹⁸ The frequency of *H. pylori* infection (70%) in our study group was compatible with that of the normal Turkish population, suggesting no increase of this infection in CIU patients. Although a higher proportion of CIU patients with confirmed *H. pylori* infection had a positive ASST than those without, the difference was not significant. The number of CIU patients with the first attack of *H. pylori* infection were not sufficient for statistical analysis, but the positivity of ASST in two of these three patients and those without *H. pylori* IgG positivity were noticeable. The lack of a clinical relation between ASST and the presence of *H. pylori* infection is a new dilemma regarding the role of *H. pylori* in the development of autoantibodies, a postulation requiring clarification by molecular analysis.

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