

Eradication Therapy for Urticaria with High Titers of Anti *H. pylori* IgG Antibody

Takashi Yoshimasu^{1,2} and Fukumi Furukawa²

ABSTRACT

Background: It is known that idiopathic chronic urticaria occasionally develops with *Helicobacter pylori* (*H. pylori*) infection, but the association between urticaria and *H. pylori* remains unknown.

Methods: We focused on the relationship between the titer of anti *H. pylori* IgG antibodies and urticaria. Sixty-five patients with idiopathic urticaria were divided into 3 groups by a difference of their titers. All patients in the high titer (≥ 40 U/ml) group underwent endoscopy of the upper gastrointestinal tract with antral biopsy for the Rapid Urease Test (RUT) or a culture test. We investigated the relationship between the efficacy of eradication therapy against *H. pylori* and urticaria.

Results: The positive rate for *H. pylori* was 100% (20/20) by RUT or culture test in the high titer group. A CR using antihistamines alone was 0% (0/20) in the high titer group, 27.2% (3/11) in the low titer group and 38.2% (13/34) in the negative group respectively. A CR or PR using antihistamines was 70% (14/20) in the high titer group, 81.8% (9/11) in the low titer group and 97.1% (33/34) in the negative group. After successful eradication therapy, the CR was increased to 56% (9/16) in the high titer group.

Conclusions: Regardless of acute or chronic urticaria, a high titer of anti *H. pylori* IgG antibody can be an indicator for undergoing upper endoscopy, and eradication therapy is strongly recommended. It will be necessary to develop diagnostic criteria for urticaria associated with *H. pylori*.

KEY WORDS

anti-*H. pylori* IgG antibody, antihistamine, eradication, *helicobacter pylori*, urticaria

INTRODUCTION

Circumscribed, raised and erythematous edema that involves the superficial portion of the dermis is known as urticaria. Urticaria rarely persists longer than 24 hours, and can be divided into two types: acute and chronic. Episodes of lesions of less than 4 weeks' duration are considered acute, whereas those persisting longer are termed chronic in Japan.¹ On the other hand, chronic urticaria is defined by the presence of urticaria for a period of six weeks or longer in Western countries.² Idiopathic chronic urticaria occasionally develops with *Helicobacter pylori* (*H. pylori*) infection. Recent observations have suggested a possible etiopathogenic role for *H. pylori* in some cases of chronic urticaria.³⁻⁸ It remains obscure whether there is an association between urticaria and

H. pylori. Urticaria caused by *H. pylori* might be diagnosed by its gastric symptoms, a high titer of anti *H. pylori* IgG antibody in the serum and the presence of urticaria. However, it is necessary to confirm the presence of *H. pylori* by the Rapid Urease Test (RUT) or a culture test, etc. using biopsy specimens of the gastric mucosa. Furthermore, if the urticaria regresses after the *H. pylori* is eradicated, the association between urticaria and *H. pylori* will be definite. There have been no reports on the relationship between urticaria with a high titer of anti *H. pylori* IgG antibodies in the serum and eradication therapy.

Herein, we describe the relationship between the titer of anti *H. pylori* IgG antibody and urticaria. Furthermore, we investigated the relationship between the efficacy of eradication therapy against *H. pylori* and urticaria.

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Conflict of interest: No potential conflict of interest was disclosed.

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Received 17 May 2013. Accepted for publication 26 July 2013.

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METHODS

Regardless of the urticaria being acute or chronic, all the patients with urticaria attending the dermatology clinic of Arida Municipal Hospital, Japan from April 1, 2008, to March 31, 2013 were screened. Sixty-five patients with idiopathic urticaria of no identifiable cause were enrolled in this study after a physical examination and laboratory tests. Anti *H. pylori* IgG antibodies in the serum were detected by enzyme-linked immunosorbent assay (ELISA). The patients with idiopathic urticaria were divided into 3 groups as follows: a high titer of anti *H. pylori* IgG antibody (≥ 40 U/ml), a low titer of anti *H. pylori* IgG antibody (≥ 10 U/ml, < 40 U/ml), and negative for anti *H. pylori* IgG antibody (< 10 U/ml). The boundary line between high and low titers was comprehensively assessed by physical examination including gastric symptoms. The high titer group included 13 patients with chronic urticaria and 7 patients with acute urticaria, and the mean age was 53.9 years old (male : female = 7 : 13). The low titer group included 4 patients with chronic urticaria and 7 patients with acute urticaria, and the mean age was 61.4 years old (male : female = 3 : 8). The negative group included 11 patients with chronic urticaria and 23 patients with acute urticaria, and the mean age was 43.5 years old (male : female = 10 : 24). The Chairman of the Ethical Committee in our hospital orally approved the protocol for the research project.

All patients started to take antihistamines orally at the first visit to our hospital.

Informed consent was obtained from all patients with a high titer of anti *H. pylori* IgG antibody and those patients with gastric symptoms whose titer was more than 20 U/ml in the low titer group. After informed consent, the patients underwent endoscopy of the upper gastrointestinal tract with antral biopsy for the Rapid Urease Test (RUT) or a culture test to identify *H. pylori*. If *H. pylori* was identified in the high titer or low titer group, eradication therapy was performed with oral antihistamines. Patients infected with *H. pylori* were given first-line therapy consisting of lansoprazole 60 mg/day, amoxicillin 1500 mg/day and clarithromycin 400 mg/day, for 7 days. If the *H. pylori* persisted after the first line therapy, then the patients were offered a second line therapy comprised of lansoprazole 60 mg/day, amoxicillin 1500 mg/day and metronidazole 500 mg/day, for another 7 days. The efficacy of the eradication therapy was assessed by a monoclonal fecal antigen assay or the urea breath test. Those patients whose titer of anti *H. pylori* IgG antibody was less than 20 U/ml in the low titer group and patients in the negative group took antihistamines only without eradication therapy.

All patients were followed up during the study duration of 1-6 months. Each patient's objective response to the treatment was judged using 3 variables:

a complete remission (CR-no need for antihistamines), a partial remission (PR- need for antihistamines at least one day to six days a week), and no remission (NR- need for antihistamines every day, or ineffective antihistamines).

Patients suffering from physical urticaria, patients less than 16 years of age, pregnant females, patients who had taken proton pump inhibitors / antibiotics within the preceding 4 weeks, and the presence of other concomitant serious medical and surgical disease were excluded from the study.

STATISTICAL ANALYSIS

χ^2 -test was used to compare an incidence of gastric symptoms and an efficacy of antihistamines alone in three groups. Wilcoxon signed-rank test was used to analyze an efficacy of successful eradication therapy in the high titer group. CR, PR and NR was scored 0, 1 and 2 respectively in Wilcoxon signed-rank test.

RESULTS

Sixty-five patients with idiopathic urticaria were enrolled in this study. The positive rate of anti *H. pylori* IgG antibodies was 47.7% (31/65) in all patients with idiopathic urticaria (high titer group: 20 cases, low titer group: 11 cases, negative group: 34 cases). Gastric symptoms including epigastric distress or gastralgia, etc. accompanied by gastritis or gastric ulcer were observed in 65% (13/20) of the high titer group, in 27.2% (3/11) of the low titer group and 14.7% (5/34) of the negative group (Table 1). There was a statistically significant difference in the incidence of gastric symptoms among the three groups ($p = 0.0006$).

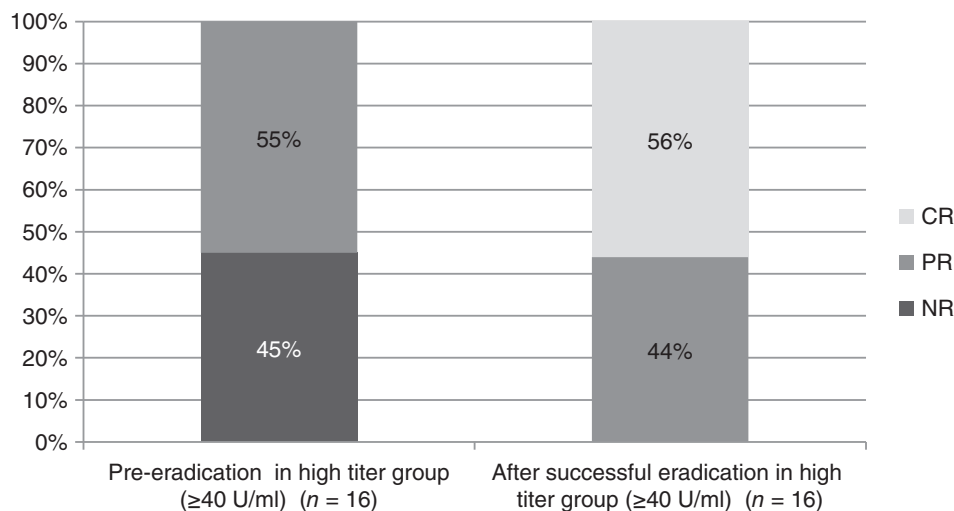
The positive rate of *H. pylori* was 100% (20/20) by RUT or culture tests in the high titer group. Three out of 11 patients showed titers of more than 20 U/ml and gastric symptoms in low titer group, and they underwent endoscopy of the upper gastrointestinal tract. The positive rate of *H. pylori* was 66.7% (2/3) by RUT in the low titer group. Negative group patients did not undergo endoscopy of the upper gastrointestinal tract. A CR following antihistamines alone was 0% (0/20) in the high titer group, 27.2% (3/11) in the low titer group and 38.2% (13/34) in the negative group respectively. A CR or PR by antihistamines alone was 70% (14/20) in the high titer group, 81.8% (9/11) in the low titer group, and 97.1% (33/34) in the negative group. The efficacy of antihistamines only in the three groups showed a statistically significant difference ($p = 0.0053$) (Table 2). The successful rate of eradication including the second line therapy was 75% (16/20) in the high titer group. Even though the second line therapy was performed, the fecal test was still positive in three out of 4 unsuccessful cases. One out of the 4 unsuccessful cases discontinued eradication therapy, because a drug eruption was observed. The cases of NR by antihistamines alone were improved after successful eradication therapy in the

Table 1 Incidence of gastric symptoms in the three groups

High titer group ($n = 20$) (≥ 40 U/ml)	Low titer group ($n = 11$) (≥ 10 U/ml, < 40 U/ml)	Negative group ($n = 34$) (< 10 U/ml)	p -value*
65 (%)	27.3 (%)	14.7 (%)	0.0006

* χ^2 -test.**Table 2** Efficacy of antihistamines in the three groups

	NR	PR	CR	p -value*
High titer group (≥ 40 U/ml) ($n = 20$)	30 (%)	70 (%)	0 (%)	0.0053
Low titer group (≥ 10 U/ml, < 40 U/ml) ($n = 11$)	18.2 (%)	54.6 (%)	27.3 (%)	
Negative group (< 10 U/ml) ($n = 34$)	2.9 (%)	58.8 (%)	38.2 (%)	

* χ^2 -test.**Fig. 1** Increase in complete remission of urticaria after successful eradication in high titer group (≥ 40 U/ml) ($n = 16$). A significant improvement was seen after successful eradication therapy. When CR, PR and NR were scored 0, 1 and 2 respectively, statistical analyses of response score using Wilcoxon signed-rank test in both groups showed statistical significance ($p < 0.001$).

high titer group.

Furthermore, after successful eradication therapy, the CR was raised up to 56% (9/16) in the high titer group, but it was 0% (0/20) by antihistamines alone, and a significant improvement was confirmed ($P = 0.0002$) (Fig. 1). In acute urticaria ($n = 5$) of the high titer group, five PR changed to five CR after successful eradication. In chronic urticaria ($n = 11$) of the high titer group, five NR and six PR changed to seven PR and four CR after successful eradication. On the other hand, one out of 2 patients who had *H. pylori* diagnosed by RUT in the low titer group did not show a CR, but underwent successful eradication therapy. Another patient with *H. pylori* in the low titer group was diagnosed with early gastric cancer plus idiopathic urticaria and showed NR to antihistamines only. After surgical resection and eradication therapy, NR changed to a CR.

DISCUSSION

Our present study showed that the positive rate of anti *H. pylori* IgG antibody in idiopathic urticaria was similar to the prevalence of *H. pylori* in chronic urticaria previously reported.⁶ On the other hand, it was also reported that a positive rate of anti *H. pylori* IgG antibody in sex and age-matched healthy control was similar to that of idiopathic chronic urticaria which is 52%.⁶ In this study, *H. pylori* infection was detected in 100% (20/20) of patients with idiopathic urticaria whose anti *H. pylori* IgG titer was more than 40 U/ml. It is still unknown whether *H. pylori* could be detected in those patients whose anti *H. pylori* IgG antibody titer was less than 20 U/ml in the low titer group, because we did not perform the upper endoscopy in such cases. It is believed that *H. pylori* was associated with the pathogenesis of chronic urti-

caria.⁵ On the other hand, there was no correlation between *H. pylori* infection assessed by the (13)C-urea breath test (UBT) and idiopathic chronic urticaria.⁹ In this study, the detection of *H. pylori* was performed by upper endoscopy in the high titer group and in some patients from the low titer group. The discrepancy observed the association between *H. pylori* and urticaria may be due to the different methods used for the detection of *H. pylori* infection.

Our study showed that idiopathic urticaria with *H. pylori* was significantly improved after eradication in the high titer group. Previous reports have also shown the resolution of urticarial symptoms after the eradication of *H. pylori*.^{4,7} On the other hand, there was a report of no correlation between eradication therapy and the regression of urticaria.¹⁰ It was also reported that the severity of urticarial symptoms was greater in the *H. pylori*-positive group than in the *H. pylori*-negative group.¹¹ They also described that the severity of the symptoms would depend on the density of the bacterial infection and the intensity of the inflammatory infiltrates in the gastric biopsy.¹¹ It was also suggested that inflammation in the gastrointestinal tract caused by *H. pylori* infection may have an important role in the etiology of chronic urticaria.³ Our present study showed a tendency that the gastric symptoms were especially pronounced in those patients with idiopathic urticaria in the high titer group of anti *H. pylori* IgG antibody as compared to the low titer or negative groups. Furthermore, the high titer group of anti *H. pylori* IgG antibody showed lower remission rates of a CR or PR by antihistamines than the low titer or negative groups. Infection with *H. pylori* could influence the efficacy of the antihistamines in urticaria. In this study, a CR was seen after successful eradication therapy in the high titer group of anti *H. pylori* IgG antibody. This suggested that eradication therapy was useful, especially for the high titer group with anti *H. pylori* IgG antibody in idiopathic urticaria. This result was supported by a recent report that some patients with anti-histamine-resistant chronic urticaria was improved after *H. pylori* eradication.¹²

The pathogenic mechanism that may exist between urticaria and *H. pylori* remains unknown. It is well known that the immunological response elicited by *H. pylori* is an important determinant of the amount of gastric mucosal damage. VacA, which is the virulent *H. pylori* cytotoxin, may precipitate the host early response to clear the bacteria, and may also contribute to the pathogenesis of *H. pylori*-induced gastritis.¹³ *H. pylori* causing inflammation in the gastrointestinal tract might facilitate the absorption of antigens or unmask existing antigens.

In this study, idiopathic acute urticaria was also associated with *H. pylori*, as well as idiopathic chronic urticaria. Eradication therapy was also useful for idiopathic acute urticaria. From our study, 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. It will be necessary to develop diagnostic criteria for urticaria associated with *H. pylori*.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Naka, Dr. Tsuchiya, Dr. Kondou, Dr. Setou and Dr. Yamashita who are the medical staff of Internal Medicine at Arida Municipal Hospital for their assistance in undergoing endoscopy of the upper gastrointestinal tract and eradication therapy.

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