Anti-*Helicobacter pylori* IgG titre in patients with chronic idiopathic urticaria and the effect of *Helicobacter pylori* eradication on urticaria

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Abstract

Introduction: Chronic urticaria (CU) is characterized by hives and pruritus lasting for more than 6 weeks. Almost half of CU cases are classified as idiopathic (CIU). The condition may be triggered by *Helicobacter pylori* (HP).
Aim: The aim of our research was to assess anti-HP IgG titre in CIU patients compared to controls and to evaluate the effect of HP eradication on urticaria.
Material and methods: The analysis covered 62 CIU patients and 55 urticaria-free individuals. Serum anti-HP IgG was performed in 50 CIU subjects and all controls. The CIU patients with gastric complaints and anti-HP IgG(+) were divided into two subgroups, of which one received standard antiurticarial treatment (A) while the other was offered standard treatment plus HP eradication (B). After a 12-month follow-up, subgroups were reviewed for treatment response.
Results: Positive anti-HP IgG titre incidence, mean and median anti-HP IgG levels in CIU patients and in the controls were as follows: 68% vs. 67.27% (χ^2 = 0.0063, p = 0.9366), 2.73 vs. 2.29 and 1.72 vs. 1.69 (p = 0.4288). AUC under the ROC curve for urticaria prediction based on anti-HP IgG level was 0.545 (SE = 0.057, 95% CI [0.434, 0.657]). On the follow-up interview, rates of improvement, no improvement and aggravation of urticaria symptoms in subgroup A were as follows: 60%, 40% and 0%, respectively, and in subgroup B: 50%, 45%, 5%, respectively (χ^2 = 0.6635, p = 0.7177, Fisher's exact test p = 1.0000).
Conclusions: Anti-HP IgG titre is similar in CIU patients and in urticaria-free controls. *Helicobacter pylori* eradication has no effect on urticaria in anti-HP IgG positive CIU patients with gastric complaints.

Key words: chronic urticaria, *Helicobacter pylori*, anti-HP IgG, eradication.

Introduction

Urticaria is characterized by raised erythematous wheals that blanch when pressed and disappear within 24 h without scarring. Skin lesions are almost invariably accompanied by severe pruritus [1-6]. Urticaria/angioedema affects approximately 20% of the general population at some point of their lives but usually presents as an acute episode resolving within a few weeks at most [1]. About 0.5% of the general population develop chronic urticaria (CU) [1, 7] with symptoms persisting for more than 6 weeks and wheals being present constantly or for most days of the week [1-6]. Visible skin lesions and itch cause distress in social, professional and domestic functioning leading to quality of life impairment comparable to that of individuals with triple coronary artery disease [4, 8, 9]. Up to 45% of CU cases are autoimmune in nature with the remaining 55% being classified as idiopathic [1, 4, 5, 7]. Occult infections, food allergies, adverse reactions to food additives, metabolic, hormonal and emotional changes, malignancies are all being investigated as possible triggering factors in the latter group [1, 4-6]. Idiopathic CU (CIU) management is confined to symptomatic treatment (antihistamines, antileukotrienes, systemic glucocorticosteroids). However, the disease tends to resolve

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spontaneously, in approximately half of cases symptoms subside within one year from diagnosis, after 5 years 85% of patients achieve remission and only in less than 5% of cases, the disease persists for more than 10 years [1].

The CU and angioedema share the same pathomechanism and commonly coexist and therefore are usually considered jointly (according to different authors, 40% [1] to 90% [3, 4] of adults with urticaria suffer from angioedema episodes concurrently).

Helicobacter pylori is microaerophilic Gram-negative spiral bacterium found in stomach whose implication in gastritis was first reported by Marshall and Warren in 1983 [10]. The HP infection is very common with a mean worldwide incidence of 60%. It is estimated that in highly developed countries it affects approximately 25% of the general population, while in the developing world, the figures exceed 80%. The incidence of HP infection is positively correlated with age and inversely with the socioeconomic status [11-14]. In Poland, HP occurs in 84% of adults and 32% of children and adolescents below 18 years of age [12-15]. The bacterium is usually acquired in childhood with most affected individuals becoming asymptomatic carriers (colonized) never developing gastritis [12]. High incidence of HP infection has recently given way to a discussion whether HP presence could be, in fact, beneficial for the host [16-18].

There are invasive and non-invasive methods of HP detection most of which make use of the unique ability of HP to produce urease (enzyme catalyzing hydrolysis of urea into carbon dioxide and ammonia). Endoscopy is considered the golden standard for diagnosing gastritis secondary to HP infection as it allows for the upper digestive tract macroscopic inspection and collection of biopsy specimens. Common non-invasive methods of HP detection comprise urea breath test, serum serology (anti-HP IgG, IgA, IgM) and HP stool antigen test. The HP eradication regimen is based on two antibiotics (two out of three: metronidazole, clarithromycin, amoxicillin) and proton pomp inhibitor twice daily for 7 days [12, 15].

The aim of our research was to assess serum anti-HP IgG titre in CIU patients compared to urticaria-free individuals and to evaluate the influence of HP eradication on the course of urticaria in those with gastric complaints and positive anti-HP IgG titre.

Material and methods

This research was approved by the institute's Ethics Committee. The database of the Clinic of Internal Medicine, Asthma and Allergy of the Medical University of Lodz was searched for patients hospitalized in 2008-2010 for chronic urticaria/recurrent angioedema. The retrieved medical records were then reviewed for the following inclusion criteria: urticaria duration of at least 6 weeks, no cause of urticaria found despite extensive laboratory and provocation testing, gastric complaint status included in the medical history, available HP serum immunoassay result (or a possibility to perform the test) and known treatment recommended at discharge. The control group comprised individuals without a history of urticaria chosen randomly from patients and healthy volunteers so as to achieve a similar demographic structure as the one in the urticaria group. All participants expressed informed consent to the study participation.

Serum anti-HP IgG assay was performed with VIDAS® *H. pylor*i IgG (HPY) from Biomerieux – automated immunoassay in VIDAS system for rapid detection of IgG antibodies specific of *H. pylori* in human serum or plasma (EDTA) by means of ELFA technique (enzyme immunofluorescence). According to the manufacturer's guidelines, results of ≥ 1 were considered positive.

The second part of our study was designed to verify whether HP eradication changes the course of CU in anti-HP IgG positive patients with gastric complaints. To do that we singled out patients reporting dyspepsia with positive immunoassay results and divided them into two subgroups (A and B). Subgroup A received only standard treatment (antihistamines, antileukotrienes, systemic glucocorticosteroids) while subgroup B was offered standard treatment plus HP eradication (metronidazole 500 mg/clarithromycin 500 mg b.i.d.+ amoxicillin 1000 mg b.i.d. and proton pomp inhibitor b.i.d. for 7 days) – Figure 1 outlines the design of this part of our study. After the follow-up period of at least 12 months from hospitalization, both subgroups were reviewed for treatment results. The patients were contacted by phone/mail and asked to fulfill a questionnaire that qualified changes in the course of urticaria in a simple 3-grade scale of patient reported outcomes: "1" improvement, "0" no change, "–1" aggravation. Patients offered eradication were also reviewed for gastric complaints withdrawal.

Statistical analysis

The results were analyzed statistically with Statistica software for Windows 9.0. The Shapiro-Wilk test was applied to check normality of data distribution. Differ-

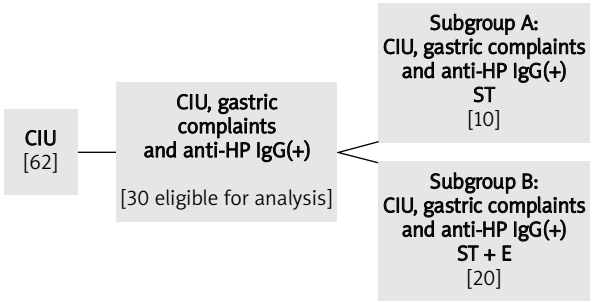

Figure 1. Study design in the second part of the study

CIU – chronic idiopathic urticaria, HP – Helicobacter pylori, anti-HP IgG(+) – positive IgG titre against Helicobacter pylori, ST – standard antiurticarial treatment, E – Helicobacter pylori eradication
Square brackets give number of subjects in each group

Table 1. Study demographics – age [years]

	Mean	SD	Minimal	Median	Maximal
Urticaria patients	47.29	16.50	17.00	49.50	83.00
Controls	46.27	13.98	18.00	47.00	82.00

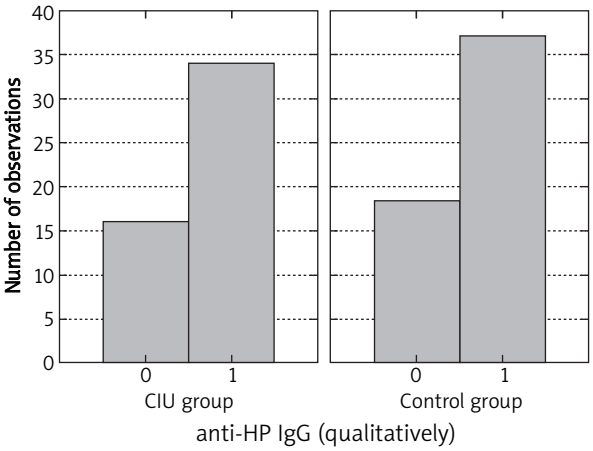

Fig. 2. Positive and negative anti-HP IgG assay distribution in CIU patients and in controls
0 – negative anti-HP IgG assay, 1 – positive anti-HP IgG assay

ences in the age distribution in both groups were tested with *U* Mann-Whitney test and *t*-Student test (conditionally). Sex distribution in both groups was compared using the fourfold table, χ^2 test and Yate's corrected χ^2 test. Differences in anti-HP IgG titre distribution were analyzed with the fourfold table and χ^2 test. Differences in serum anti-HP IgG level were analyzed with the *U* Mann-Whitney test (hypothesis of differences in distribution) and *t*-Student test (conditionally, hypothesis of differences in mean values). Hypothesis of predicting urticaria based on the anti-HP IgG level was additionally tested with ROC curve. The correlation between change of health status and the applied treatment was checked with the fourfold table, χ^2 test and Fisher's exact test. Value of *p* of less than 0.05 was considered significant and less than 0.01 – highly significant.

Results

Sixty-two patients with chronic urticaria met our study inclusion criteria. The control group comprised 55 urticaria-free individuals – the demographics of both groups are

Table 3. Anti-HP IgG level

	Mean	SD	Minimal	Median	Maximal
Urticaria patients	2.73	2.67	0.06	1.72	9.35
Controls	2.29	2.22	0.02	1.69	7.95

Table 2. Study demographics – sex

	Females *n* (%)	Males *n* (%)	Total
Urticaria patients	53 (85.48)	9 (14.52)	62
Controls	34 (61.82)	21 (38.18)	55

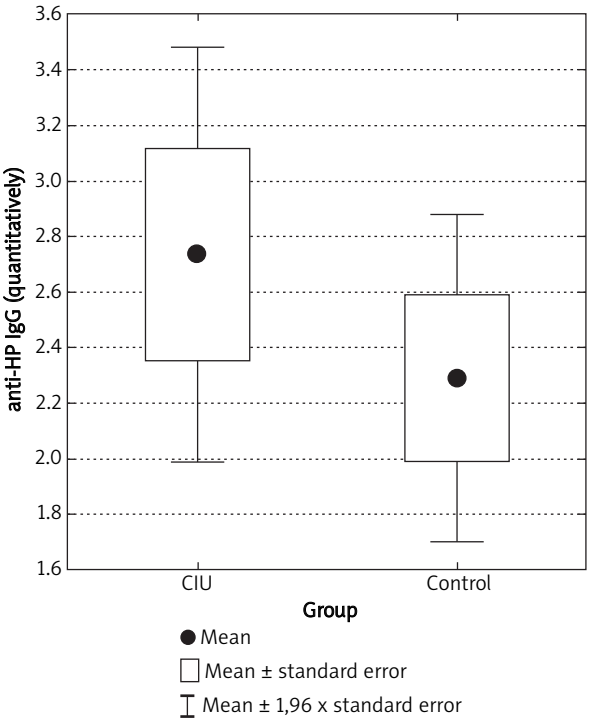

Fig. 3. Mean anti-HP IgG level in CIU patients and in the control

given in Tables 1 and 2. All parameters (except for age in the control group) followed non-normal distribution pattern and both groups were homogeneous for age (*U* Mann-Whitney test $p = 0.5775$, *t*-Student test $p = 0.7215$).

In the urticaria group, the serum anti-HP IgG immunoassay was performed in 50 persons, of which 33 (68%) showed positive titre. In the control group, 37 persons out of 55 were found to be anti-HP IgG positive (67.27%) (positive/negative assay distribution in both groups is shown in Figure 2). No significant association between positive anti-HP IgG titre and urticaria was observed ($\chi^2 = 0.0063$, $p = 0.9366$).

Considering data from the literature we also compared the actual anti-HP IgG level in both groups. In the urticaria group, both mean and median anti-HP IgG levels were slightly higher than in the controls (mean: 2.73, SD = 2.67, median: 1.72 vs. 2.29, SD: 2.22, median: 1.69) but the values did not reach statistic significance ($p = 0.4288$ in the *U* Mann-Whitney test and $p = 0.3589$ in the conditionally used *t*-Student test) – the results are presented in Figure 3 and Table 3. The hypothesis of the

association of anti-HP IgG level and chronic urticaria was additionally tested with a ROC curve. Its shape and AUC of 0.545 (SD = 0.057, 95% CI 0.434-0.657) confirm that predicting urticaria occurrence based on anti-HP IgG level is only negligibly better than random classification – the ROC curve and level of false classifications are shown in Figures 4 and 5, respectively.

Thirty-three patients entered the second part of our study but eventually 3 were lost to follow-up. Of the remaining 30 patients, 10 were given only standard treatment (subgroup A) and 20 received standard treatment plus HP eradication (subgroup B). At the follow-up interview, in all patients who received eradication, gastric complaints subsided. As for the urticaria: in subgroup A – 6 patients reported improvement, 4 – no change and there were no cases of urticaria aggravation, whereas in subgroup B the figures were as follows: 10, 9 and 1, respectively. Results are presented in Table 4. No statistically meaningful association between applied treatment and change in the chronic urticaria status was found ($\chi^2 = 0.6635$, d$f = 1$, $p = 0.7177$, Fisher's exact test $p = 1.0000$).

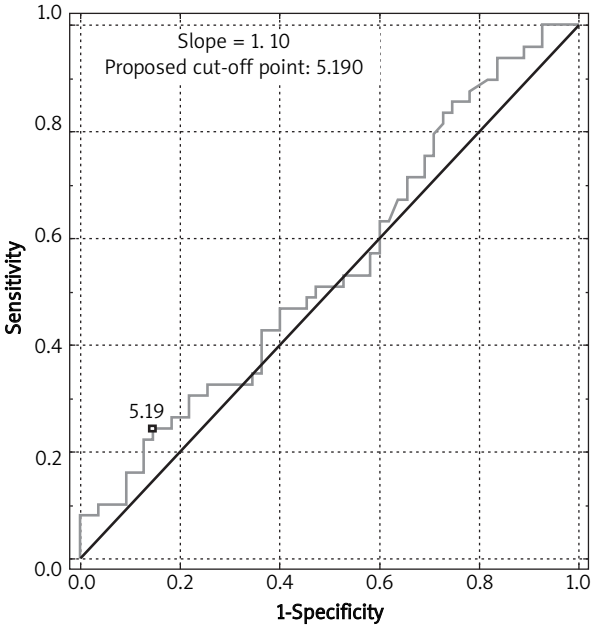

Fig. 4. ROC curve. Predicting urticaria based on anti-HP IgG titre is negligibly more accurate than typing based on random classification. AUC = 0.545 (SE = 0.057, 95% CI [0.434, 0.657])

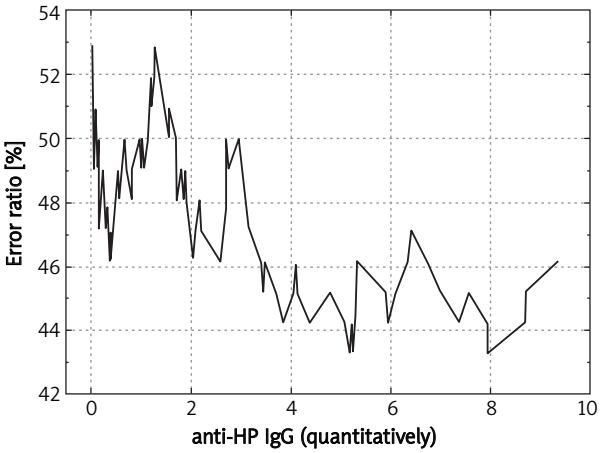

Fig. 5. Level of error classifications based on anti-HP IgG level is high and reaches 53%

Discussion

Chronic idiopathic urticaria is a frustrating condition for both the patient and the treating doctor. Given the limitations and risks of the available symptomatic treatment for chronic urticaria, the very idea of identifying a simple and curable cause like infection seems appealing.

The possibility of chronic urticaria being an extragastric manifestation of HP infection has been discussed for at least 15 years [1, 13, 14, 20-25]. Unfortunately, conclusive data are lacking, there are equally many reports advocating the association [26-35] as those denying it [36-43]. Kaplan notes that if HP could in fact trigger urticaria than – considering the rate of HP infection worldwide – the incidence of chronic urticaria would far exceed the reported level of 0.5% [1]. Numerous trials incorporating HP eradication into urticaria treatment emerged and in 2003 Federman *et al*. published the first systematic review with joint analysis of data from the available studies [44]. The results were very promising, it was shown on a large group of patients (altogether 266 urticaria cases reviewed) that HP eradication results in urticaria resolution in a highly meaningful manner

Table 4. Change in urticaria symptoms depending on the therapeutic group on the follow-up

	Improvement *n* (%)	No improvement *n* (%)	Aggravation *n* (%)	Total
Standard treatment (subgroup A)	6 (60)	4 (40)	0 (0)	10
Standard treatment + *Helicobacter pylori* eradication (subgroup B)	10 (50)	9 (45)	1 (5)	20
Total	16	13	1	30

(p = 0.005!). Six years later, Wedi *et al*. provided another comprehensive overview of recent evidence on the subject and recommended that HP testing should be a part of routine work-up in chronic urticaria patients [45]. In 2010, clinical studies on the effectiveness of HP eradication in chronic urticaria were re-evaluated by Shakouri *et al*., this time using the GRADE approach [14] which led to a contrary conclusion. Of the 106 reports found in the medical databases, only 19 fulfilled inclusion criteria for the analysis and of those, 10 were in favor of the anti-HP treatment while 9 proved the opposite. Significant data diversification (e.g. different urticaria improvement definitions, eradication regimens, follow-up times) hindered drawing unequivocal conclusions. Unfortunately, each of the 19 studies had certain methodological shortcomings which considerably reduced the strength of the final recommendation. In the end, the authors stated conservatively that large, methodologically sound, double-blind and controlled studies are needed to give a definite answer and that so far only a weak recommendation favoring eradication can be given.

Our study showed no association between serum anti-HP IgG and chronic urticaria. In terms of statistical significance, anti-HP IgG status in the urticaria group differed from the controls neither qualitatively nor quantitatively. ROC analysis and AUC proved that predicting urticaria based on anti-HP IgG results is only slightly better than random classification. Perhaps increasing the number of observations would prove otherwise.

HP infection detection in CIU patients is problematic as the reference methods used for HP status determination in the general population are not quite fit for urticaria patients whose gastric complaints' intensity hardly ever justify invasive diagnostic procedures. Upper endoscopy carries risks (e.g. hospital-acquired infection, digestive tract rupture) outweigh benefits in individuals presenting without severe dyspepsia as it is in most cases of CIU. The urea breath test on the other hand involves radioactive medium consumption and is therefore unsuitable for women of childbearing potential. Both procedures make the diagnostic process costly and time consuming. HP stool antigen test is rarely done outside the gastroenterology setting. Serum anti-HP IgG assay is unsuitable for determining active infection or for evaluation of eradication success but serves well as a screening tool as it is non-invasive, cheap and easily accessible in any allergology, dermatology or primary care site. For those reasons it is often chosen for HP detection in urticaria studies [30, 31, 41, 46].

The second part of our study showed no influence of HP eradication on the urticaria course in CIU patients with gastric complaints and positive anti-HP IgG titre. However, there were isolated cases of successful urticaria resolution after HP eradication but only in patients with severe dyspepsia and HP(+) peptic ulcers confirmed on endoscopy. It is possible that only active HP infection manifests as urticaria and the effectiveness of eradication is limited to those cases. HP infection could also be a triggering factor for autoimmune host response that carries on despite the primary offending agent removal [4, 46]. Indeed, in some patients, urticaria seems to be autoimmune in nature [4, 47-51]. Functional antibodies against high affinity IgE receptor FcεR1 are found in 30% to 50% of urticaria cases [4, 49-55]. No influence of eradication on urticaria may also result from HP therapy resistance and tendency to rapid recurrences after successful treatment. On the other hand, antibiotics used in eradication may eliminate some other microorganisms that we are not yet aware of – some researchers have observed a similar urticaria remission rate after prescribing eradication antibiotics to HP negative patients [25].

Conclusions

Anti-HP IgG titre is similar in CIU patients and in urticaria-free controls. HP eradication does not change the urticaria course in CIU patients with gastric complaints and positive anti-HP IgG titre and therefore should not be a part of routine management. Antibiotic treatment exposes the patient to additional burdens (costs, drug adverse effects, antibiotic resistance etc.) while providing uncertain benefits. HP eradication may be suitable for urticaria patients with objectively confirmed (preferably on endoscopy) concomitant HP positive active gastritis. A decision to implement invasive diagnostic procedures in CIU patients requires careful individual risk-benefit assessment.

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