

***Helicobacter pylori* Infection as a Triggering Factor of Attacks in Patients with Hereditary Angioedema**

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Keywords

abdominal attack, *Helicobacter pylori* infection, hereditary angioedema.

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Performed within the framework of the PREHAEAT project (QLG1-CT-2002-01359) of the European Union.

Abstract

Background: *Helicobacter pylori* infection is considered among the causative factors of urticaria and angioedema. Having conducted a study on 65 patients, Hungarian authors reported in 2001 that successful eradication of *H. pylori* is followed by a significant reduction in the number of attacks in patients with hereditary angioedema (HAE). The present study aimed to reinvestigate the relationship between *H. pylori* infection and the attack rate in the framework of an international collaborative study.

Materials and methods: Within the framework of the PREHAEAT project launched by the European Union, further 152 patients were studied in seven collaborating centers, and participants of the earlier study were followed up in order to detect any relationship between *H. pylori* infection and the occurrence of attacks in patients suffered from HAE.

Results: The proportion of patients experiencing frequent (≥ 5 per year) abdominal attacks was higher ($p = .002$) among the *H. pylori*-infected participants of the international study who underwent eradication as compared to the rest of patients. Successful eradication of *H. pylori* significantly ($p = .0006$) reduced the number of attacks in these patients as well.

Nine subjects of the previous Hungarian study who underwent eradication therapy for dyspepsia were followed up for an additional 4 years. In these patients, attack frequency remained consistently low.

Conclusions: As shown by experience from the Hungarian and the international trial, the number of frequent, edematous abdominal attacks may decrease substantially following the eradication of *H. pylori* from HAE patients infected with this pathogen. Therefore, screening of patients with HAE for *H. pylori* infection seems warranted. Eradication of *H. pylori* may lead to a marked reduction in disease severity.

Introduction

Hereditary angioedema (HAE) is caused by the deficiency of the C1-inhibitor (C1-INH), which is inherited as an autosomal dominant trait [1]. The lack of this regulatory protein results in the spontaneous activation of the classical pathway of the complement and contact (coagulation, fibrinolytic, kinin) systems [2]. Activation is associated with the release of vasoactive mediators (e.g. bradykinin) with consequent effusion from the intravascular space – these processes produce edema. HAE is characterized by paroxysms of subcutaneous and submucosal edema

formation. The latter may involve the laryngeal mucosa and thereby cause suffocation [3]. Edema of the intestinal mucosa may mimic an acute abdominal catastrophe and, accordingly, patients afflicted by this condition frequently undergo unwarranted surgery [4]. Moreover, intense abdominal pain often interferes with social and occupational activities.

As suggested by observational evidence, a variety of factors can precipitate attacks, including mechanical trauma, dental surgery, or surgical interventions in the head and neck region, mental stress, infections, hormonal changes, and treatment with certain drugs [5].

Table 1 Demographic data of patients with hereditary angioedema enrolled in the study in seven countries

Country	Number of patients	Males	Females	Average age
Denmark	45	20	25	38.07 (2–69)
France	3	0	3	28.33 (20–40)
Germany	33	13	20	39 (8–77)
Hungary	48	21	27	28.02 (1–72)
Italy	1	1	0	30
Switzerland	4	2	2	47 (28–53)
UK	18	7	11	32.33 (4–73)
Σ	152	64 (42.1%)	88 (57.9%)	34.41 (1–77)

After the demonstration of the link between *H. pylori* infection and gastric ulcer or chronic gastritis [6,7], an increasing number of publications discussed the influence of this Gram-negative bacterium on other diseases. This relationship has been observed also in cardiovascular, neurologic, and dermatologic disorders [8–13]. In 1990, Rais et al. [14] brought some evidence for a role of *H. pylori* infection in the frequent recurrence of abdominal edematous attacks in a patient with HAE. Our workgroup reported a case of acquired angioedema accompanying *H. pylori* infection in 1999 [15]. In a study conducted on 65 Hungarian patients in 2001 we found a significantly higher incidence of edematous abdominal attacks in the history of patients with *H. pylori* infection. Successful elimination of this pathogen resulted in a statistically significant reduction of the number of edematous attacks [16]. In view of the foregoing, the present study aimed to reinvestigate the relationship between *H. pylori* infection and the attack rate in the framework of an international collaborative study.

Methods

Two patient groups were studied. First, 152 patients were enrolled from seven European countries that collaborated in the study implemented within the framework of the PREHAEAT project (Novel Methods for Predicting Preventing and Treating Attacks in Patients with Hereditary Angioedema QLGI-CT-2002-01359) of the European Union. Inclusion criteria were as follows: HAE diagnosis, registered number of subcutaneous, abdominal, laryngeal attacks in last year, and verified or excluded *H. pylori* infection. As exclusion criteria, we excluded from the international study the Hungarian patients who participated in the previous Hungarian study in 2001. These patients were the attendants of the follow-up trial. No other patients were excluded from the study.

Patients were regularly cared in the department of one of the coauthors of the paper. Second, 65 participants of the Hungarian 2001 study [16] were followed up for the

subsequent 4 years and their clinical data were recorded in the Hungarian HAE Registry.

PREHAEAT is intended for improving the quality of life of patients with HAE by expanding research, and facilitating its exploitation by the users. This project is expected to identify novel laboratory markers suitable for predicting attack frequency. From Hungary, new cases identified after the conclusion of the previous study were entered into the international register.

Demographic data of the 152 participants of the study are detailed in Table 1.

The principal investigators of individual study centers obtained a detailed history from patients managed at their institutions. Along with clinical and laboratory parameters, these historical data were uploaded to the international HAE Registry, using a password-protected webpage (www.haeregister.org). Epidemiologic information of patients enrolled into work package no. 4 (*H. pylori* susceptibility to abdominal attacks) was retrieved from the registry and subjected to statistical analysis along with clinical data pertinent to the study.

Active *H. pylori* infection was verified in the international population of HAE patients with the C¹⁴-urea breath test alone or in combination with testing for anti-*H. pylori* IgG antibodies. Eradication was performed at each center according to the ongoing local protocols and in conformity with international guidelines. The following combinations were used: a proton pump inhibitor (esomeprazole: 5 patients; lansoprazole: 5 patients; omeprazole: 16 patients; pantoprazole: 1 patient; and pantoazole: 1 patient) with two different antibiotics (amoxicillin + clarithromycin: 15 patients; amoxicillin + metronidazole: 4 patients; clarithromycin + metronidazole: 9 patients). In one case, eradication was initiated by the family practitioner with an unspecified combination.

A follow-up breath test was performed at the next control visit (at least 6 weeks later). In order to verify the effect of eradication of *H. pylori* infection on angioedema recurrences, the number of registered edematous (subcutaneous,

Table 2 Frequency of abdominal attacks in patients with hereditary angioedema who underwent or did not undergo *H. pylori* eradication treatment in the year before the study

Frequency of abdominal attacks per year	No eradication Number of patients (%)	Eradication Number of patients (%)	Σ Number of patients (%)
0 or one attack every second year	31 (26.3)	2 (6.7)	33 (22.3)
1	20 (16.9)	3 (10.0)	23 (15.5)
2	11 (9.3)	1 (3.3)	12 (8.1)
3–4	16 (13.6)	4 (13.3)	20 (13.5)
5–8	19 (16.1)	6 (20.0)	25 (16.9)
9–12	17 (14.4)	7 (23.3)	24 (16.2)
13–20	1 (0.8)	3 (10.0)	4 (2.7)
> 20	3 (2.5)	4 (13.3)	7 (4.7)
Σ	118 (100.0)	30 (100.0)	148 (100.0)

χ^2 test: $p = .0337$.

laryngeal, and abdominal) attacks experienced during the 1-year period before eradication was compared with the same data recorded for 12 months after eradication in patients with negative breath test at 6 months.

The accumulated data were analyzed using SPSS for Windows software package (version 13.0, SPSS Inc., Chicago, IL, USA).

Results

The Prevalence of *H. pylori* Infection Within the International Population

The international study enrolled 152 patients from seven countries; the demographical data of the study population are summarized in detail by Table 1. Edematous abdominal attacks were identified in the history of 125 patients (82.2%); 39.5% (60/152) of these patients experienced five or more abdominal attacks per year (Table 2). Abdominal attacks were defined as excruciating, colicky abdominal pain, nausea, and vomiting and or diarrhea without fever that is caused by swelling in the intestinal wall. These symptoms lasted 1–2 days, resolved spontaneously or after administering symptomatic drugs or C1 inhibitor concentrate.

Of the 152 patients, 139 were available for serologic testing of *H. pylori* IgG, of which 61 (43.9) resulted positive. Thirty of the 61 *H. pylori* IgG-positive patients accepted eradication therapy after infection was confirmed by C¹⁴-UBT. We asked the permission of patients to undergo eradication therapy.

Eradication was successful in 28 patients and the data recorded during their 12-month follow up were available. During the 1 year of follow up, as compared to the attack rate recorded during 12 months before eradication, attack frequency decreased in 19 patients, did not change in seven patients, and increased in two patients. Wilcoxon's non-

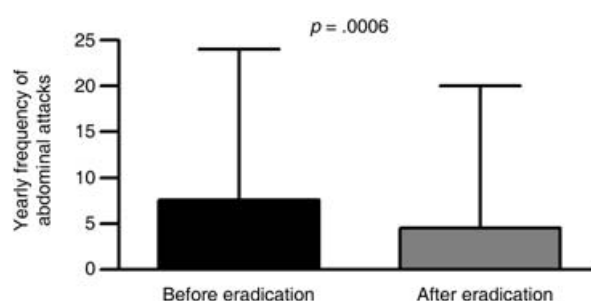


Figure 1 Yearly rate of abdominal attacks in 28 *H. pylori*-infected patients with hereditary angioedema before and after successful eradication treatment. p -value for repeated measure nonparametric (Wilcoxon) test is indicated.

parametric test revealed a statistically significant ($p = .0006$) reduction in the number of abdominal attacks (versus baseline) during the 1-year period following eradication compared to data from the 12-month period preceding eradication (Fig. 1). The total number of abdominal attacks decreased significantly ($p = .0006$), whereas no significant change could be demonstrated in the occurrence of laryngeal ($p = .156$) or subcutaneous ($p = .794$) attacks (Table 3).

Follow up of the Participants of the Earlier Hungarian Trial

Our report published in 2001 [16] identified a subset of nine patients (out of 65 patients with HAE) who had had experienced frequently recurring abdominal edematous attacks accompanied by dyspepsia, despite uninterrupted and previously effective long-term pharmacotherapy. All of these nine patients were infected with *H. pylori*. Successful eradication of this pathogen reduced the cumulative number of abdominal attacks to one from 28

Table 3 Number of attacks in *H. pylori*-infected patients with hereditary angioedema before and after eradication therapy

	Country	Number of attacks before eradication			Treatment before eradication		Number of attacks after eradication			Treatment after eradication	
		Abdominal	Laryngeal	sc	Type of drug	Daily dose (mg)	Abdominal	Laryngeal	sc	Type of drug	Daily dose (mg)
Patient 1	Germany	12	0	10	Danazol	33	1	0	4	Danazol	33
Patient 2	Germany	24	0	18	0	0	12	0	15	0	0
Patient 3	Germany	5	0	5	0	0	2	0	6	0	0
Patient 4	Germany	12	0	10	Danazol	100	5	1	8	0	0
Patient 5	Germany	15	0	10	0	0	18	0	18	0	0
Patient 6	Germany	18	0	12	0	0	5	0	10	0	0
Patient 7	Germany	8	0	6	0	0	3	0	7	0	0
Patient 8	Hungary	7	0	2	Danazol	100	7	0	1	Danazol	100
Patient 9	Hungary	15	0	2	Danazol	200	6	0	0	Danazol	200
Patient 10	Hungary	6	0	5	Danazol	50	3	0	11	Danazol	50
Patient 11	Hungary	3	0	12	0	0	1	0	15	0	0
Patient 12	Hungary	1	0	0	0	0	0	0	0	0	0
Patient 13	Hungary	1	0	1	0	0	0	0	4	0	0
Patient 14	Hungary	0	0	0	0	0					
Patient 15	Hungary	0	0	0	0	0	0	0	0	0	0
Patient 16	Hungary	2	1	2	Danazol	100	1	0	1	Danazol	100
Patient 17	Hungary	5	0	12	Tranexamic acid	1000	5	0	2	Tranexamic acid	1000
Patient 18	UK	1	0	1	Stanozolol	4	1	0	40	Stanozolol	4
Patient 19	UK	20	4	20	C1 inhibitor	300 IU*	20	2	5	C1 inhibitor	300 IU*
Patient 20	Denmark	12	0	12	0	0	0	0	10	0	0
Patient 21	Denmark	11	0	10	0	0	10	0	9	0	0
Patient 22	Denmark	2	0	0	0	0	0	0	0	0	0
Patient 23	Denmark	3	0	2	0	0	10	0	4	0	0
Patient 24	Denmark	1	0	10	0	0	0	0	7	0	0
Patient 25	Denmark	3	0	3	Danazol	90	1	0	0	Danazol	90
Patient 26	Denmark	1	1	13	0	0	0	0	6	0	0
Patient 27	Denmark	4	1	2	Danazol	200	2	0	1	Danazol	150
Patient 28	Italy	10	1	8	0	0	10	0	8	0	0
Total		213	8	206			127	3	222		
Median (25–75 Interquartile range)		4 (1–11.5)	0 (0–0)	5 (1–11)			2 (0–6)	0 (0–0)	6 (1–10)		

Wilcoxon nonparametric test. sc, subcutaneous.

Number of abdominal attacks: before eradication/after eradication: $p = .0006$.Number of laryngeal attacks: before eradication/after eradication: $p = .156$.Number of subcutaneous attacks: before eradication/after eradication: $p = .794$.Dose of prophylactic drugs: before eradication/after eradication: $p = .500$.

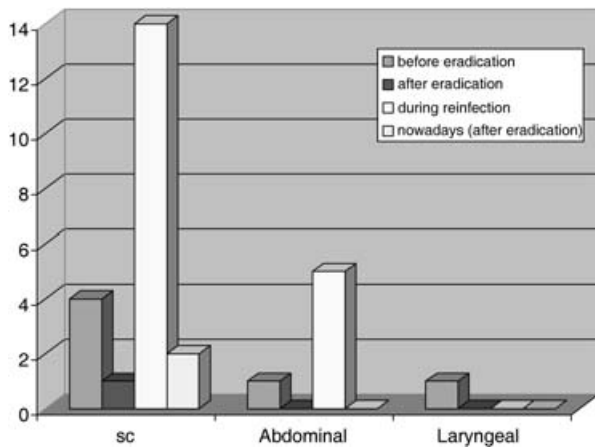


Figure 2 Changes in number of attacks per year in an *H. pylori*-infected patient with hereditary angioedema after eradication, reinfection, and repeated eradication treatment.

per year, whereas the total number of attacks decreased to 19 from 100 [16].

These patients were followed up for an additional 4 years. Since one patient died in the meantime, only eight patients could be followed throughout. Neither the number nor the localization of edematous attacks changed in these patients during this period. No dosage adjustment of drug prophylaxis was necessary (Table 4). The number of attacks sustained during the 12-month period before eradication was compared to the mean number of attacks occurring during the 4-year-long follow up. Statistical analysis performed using Friedman's ANOVA test followed by Dunn' post-test revealed a significant reduction of total attack number ($p < .01$) and the number of abdominal attacks ($p < .01$), along with the dose requirements of prophylactic agents ($p = .05$). On the other hand, no differences were found when the period just after eradication and the follow-up period were compared (Table 4). In addition, C1-INH activity, which was found to be 25.8% (15.5–53.2) (median [interquartile range]) after eradication, significantly ($p = .039$) increased to 75.6% (66.0–85.0) during the follow-up period.

During follow up, a 54-year-old subject was re-infected by *H. pylori*, as demonstrated by the C¹⁴-UBT. The incidence of edematous manifestations increased during the period of active infection, but successful eradication reduced and stabilized the number of symptoms (Fig. 2).

Discussion

Apart from peptic ulcer and chronic gastritis, where its role is strongly proven, *H. pylori* infection has been implicated as cofactor in several pathologic conditions and in patients with HAE, it seems to precipitate attacks [14,16]. Nevertheless,

validation of these findings requires confirmation by different observers as recommended in a recent review article [17]. The present study was undertaken to confirm, in the setting of a multicenter international group, that eradication of *H. pylori* infection reduces disease severity in patients with HAE. We found a strong positive correlation between eradication of *H. pylori* infection and decrease in the frequency of abdominal attacks as compared to the pre-eradication period in 19 of 28 patients of the international study. Moreover, according to the evidence accumulated during 4 years of follow up of eight Hungarian patients, this reduction seems to be sustained and associated with increase in the C1-INH activity as well. Interestingly enough, in contrast to the sharp decrease in the abdominal attack rate after eradication of *H. pylori*, this treatment did not significantly decrease the frequency of the laryngeal or subcutaneous attacks in the multicenter study. We postulate that exacerbations of acute hereditary angioneurotic edema might be triggered by activation of humoral immune responses against *H. pylori*, leading to depletion of C1-INH. This process might result in the uncontrolled activation of complement and other plasma enzyme systems. Direct local mucosa damage due to cell death can generate activation of complement and other contact systems.

As suggested by recent data, the eradication of *H. pylori* accomplishes marked clinical improvement in another disease, i.e. idiopathic thrombocytopenic purpura (ITP) as well. After eradication, a significant increase in platelet count was observed by several groups [18–21].

At present, we are unable to give a definite explanation for our findings. The situation is similar in the case of ITP [19,21] and other extra-gastric diseases evidently associated with *H. pylori* infection such as chronic idiopathic urticaria [22], Schönlein-Henoch purpura [23], or rosacea [24]. Stasi et al. [19] observed the decrease of platelet-associated immunoglobulin levels after *H. pylori* eradication, and this might be explained by the reduced formation of antiplatelet antibodies induced by *H. pylori*. Suzuki et al. [21] reported that high anticytotoxin-associated gene A (CagA) antibody titer is a good predictor of platelet recovery. In our previous study [16] we also found the number of abdominal attacks occurring over a lifetime to be significantly greater in patients infected with CagA-positive, than in those infected by CagA-negative *H. pylori* strains. In their immunoproteomic investigation conducted in *H. pylori*-infected patients with rosacea and chronic urticaria, Mini et al. [25] found some disease-specific antibodies against different *H. pylori* antigens. In the case of HAE, it is tempting to speculate that attacks – and abdominal attacks in particular – might be triggered by the activation of humoral immune responses against *H. pylori*, leading to the depletion of the C1-INH. This process might result in uncontrolled activation of the complement and further plasma enzyme systems.

Table 4 Number of attacks in *H. pylori*-infected patients with hereditary angioedema (HAE) before and after eradication therapy as well as during the 4-year follow-up period

	HAE attack frequency (number per year)											
	Before eradication				After eradication				During the last 4 years			
	sc	Laryngeal	Abdominal	Drug dose (danazol mg/day)	sc	Laryngeal	Abdominal	Drug dose (danazol mg/day)	sc	Laryngeal	Abdominal	Drug dose (danazol mg/day)
Patient 1	8	0	6	100	4	0	0	50	1	0	0	50
Patient 2	6	1	6	200	2	0	0	50	6	0	0	50
Patient 3	10	0	5	200	3	0	0	100	2	0	0	100
Patient 4	12	0	1	3 ^a	1	0	0	2 [*]	0	0	0	50
Patient 5	8	0	3	200	2	0	0	200	0	0	0	100
Patient 6	4	1	1	100	1	0	0	50	2	0	0	100
Patient 7	11	0	3	200	0	0	1	100	5	0	1	100
Patient 8	7	0	1	100	2	0	0	100	2	0	0	0
Patient 9**	3	1	2	200	2	1	0	100				
Total	69	3	28		17	1	1		18	0	1	
Median	8	0	3	200	2	0	0	100	2	0	0	75
(25–75 interquartile range)	(5–10)	(0–1)	(1–5)	(100–200)	(1–2.5)	(0–0)	(0–0)	(50–100)	(0.25–4.25)	(0–0)	(0–0)	(50–100)

^atranexamic acid (g/day), **Died during the follow-up period. sc, subcutaneous.

ANOVA Friedman test, Dunn post-test.

Total number of attacks: before eradication/during last 4 years: $p < .01$; after eradication/last 4 years: $p > .05$.

Total number of abdominal attacks: before eradication/during last 4 years: $p < .01$; after eradication/last 4 years: $p > .05$.

Dose of prophylactic drugs: before eradication/during last 4 years: $p < .05$; after eradication/last 4 years: $p > .05$.

Whatever the mechanism of the association between *H. pylori* infection and HAE attacks, screening for *H. pylori* infection and eradication of this pathogen from infected patients with frequently recurring abdominal symptoms both seem warranted. Importantly, reinfection should always be considered when relapse ensues during the years after eradication. These interventions can be expected to reduce attack frequency and thereby to improve the patients' quality of life.

This study was supported by the grants PREHAET QLG1-CT-2002-01359 and ETT 194/2003 and OTKA T046496 KON, and by a grant from the Swiss Staatssekretariat für Bildung und Forschung (SBF 02.0347). The authors wish to thank the invaluable assistance of Éva Németh MD in the computerized recording of study data.

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