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Gastritis Can Cause and Trigger Chronic Spontaneous Urticaria Independent of the Presence of *Helicobacter pylori*

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Urticaria · *Helicobacter pylori* · Inflammation · Gastritis

Abstract
Background/Aim: In chronic spontaneous urticaria (CSU), *Helicobacter pylori* (HP) has been discussed as a cause, but it is unknown whether the bacterium itself or concomitant inflammation is causing the urticaria. Our aim was to investigate HP and upper gastrointestinal lesions as signs of inflammation independently of each other in the pathogenesis of CSU. ***Methods:*** A total of 36 prospectively enrolled CSU patients from Moscow were investigated by gastroscopy and screened for the presence of HP and/or upper gastrointestinal lesions. Those having a positive result were treated according to the Maastricht III recommended guidelines for eradication therapy, and success was assessed by a follow-up gastroscopy. Simultaneously, the activity of CSU was measured before and after therapy of the gastrointestinal condition. ***Results:*** HP was observed in 26 of the 36 patients. Erosions or ulcers were found in 18 of the 36 patients, 14 of whom were also positively tested for HP. There was a significant difference in improvement of urticarial symptoms between those who succeeded in healing the erosions and those who did not succeed ($p < 0.01$) independent of the presence of HP. No significant difference in symptom relief was observed between those who had successful eradication and those in whom HP eradication failed. ***Conclusions:*** Upper gastrointestinal inflammatory disorders can cause CSU and trigger exacerbations independently of HP. This might imply that also in HP-positive patients, urticaria is not based on an immunological reaction against the germ but rather on the underlying inflammation. These findings also strengthen the importance of a gastroenterological workup of patients with CSU.
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Introduction

Urticaria is defined as the sudden appearance of wheals, angioedema, or both, presenting in different subtypes. The disease is known since ancient times, but its

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etiology and pathogenesis are only partly understood and still a matter of research [1, 2]. With regard to chronic spontaneous urticaria (CSU), a number of factors contributing to the pathophysiology of the disease in the individual patient have been discovered. These include autoimmunity, pseudoallergic reactions against NSAIDs (nonsteroidal anti-inflammatory drugs) and food, and infections (viral, parasitic, and bacterial), with their prevalence depending largely on regional factors.

Especially in Europe, the role of *Helicobacter pylori* (HP) infection has been a matter of research, and an investigation of its presence and its role in CSU using a gastroenterological workup has been recommended. Subsequent research rendered conflicting results: some researchers could show a beneficial effect of HP eradication [3–6], others questioned it [7–11] and the need to send CSU patients to gastroscopy was disputed. In the current guidelines, HP is considered to have a possible causative role in selected patients. Testing for HP antigen in stool is therefore part of the recommended extended diagnostic program for CSU [1]. However, it remains unclear whether the HP antigen itself or the inflammation it causes is responsible for the association with CSU. As other gastrointestinal disorders such as bile reflux and atrophic gastritis – as well as other disorders of the liver and bile ducts, esophagus, stomach, and duodenum – have been linked to urticaria too [12], the evidence suggests that inflammation of the gastrointestinal tract itself can be a cause of urticaria.

This study was thus designed to investigate the role of HP and gastric inflammation (represented by erosions/ulcers) in eliciting CSU independently of each other.

Methods

CSU patients from Moscow were included and examined by gastroscopy. Based on informed consent, 36 patients were enrolled (20 women [55.6%] and 16 men [44.4%]; mean age 41.8 years [range 21–70]). All 36 patients were thoroughly questioned for possible triggers of their symptoms, and especially for present or past upper gastrointestinal disorders/symptoms. Disease activity was measured using the Urticaria Activity Score (UAS). Complete remission was defined as an UAS7 score of 0, partial success as an UAS7 score ≤6.

On each of the 36 patients, primary upper gastrointestinal endoscopy (UGIE) with HP determination by PCR was performed. The patients were treated depending on the presence of HP and erosions/ulcers according to the Maastricht III recommended guidelines [13], as shown in Table 1. If HP was observed (with or without erosions/ulcers), eradication therapy was prescribed. HP-positive but erosion/ulcer-negative patients received 1,000 mg amoxicillin, 500 mg clarithromycin, and 20 mg omeprazole twice daily for 10 days. Patients tested positively for HP and showing erosions/ulcers were treated with the same scheme, with the addition of 480 mg bismuth tripotassium dicitrate daily for 10 days.

A simple antisecretory and antacid therapy was prescribed to HP-negative but erosion/ulcer-positive patients, consisting of 20 mg omeprazole twice daily and 1,000 mg hydrotalcite (aluminum magnesium hydroxide carbonate hydrate) 4 times daily for 14 days.

A strict diet with avoidance of spicy, acidic, fatty, and fried food, sweets, and alcohol was also recommended to all patients.

On patients initially presenting with erosions/ulcers (HP positive and negative), a second UGIE (UGIE-2) was performed immediately after eradication or a 2-week course of antisecretory treatment. If gastric erosions/ulcers were observed again on UGIE-2, prolongation of the strict diet as well as 20 mg omeprazole intake twice daily were prescribed, with another control UGIE after 2–6 weeks. In gastric erosion/ulcer-negative but HP-positive patients, eradication therapy was prescribed and a control UGIE-2 recommended. To all patients with gastroesophageal reflux disease or duodenogastric reflux without gastric erosions/ulcers, a 2-month omeprazole treatment at 20 mg twice daily with a strict diet was prescribed.

After ineffective eradication and no effect from omeprazole, 1 patient with duodenogastric bile reflux was treated with ursodeoxycholic acid (patient 24). All patients took antihistamines when needed.

Remission of CSU was determined after UGIE-2 or at the end of medication therapy. The remission data were independently related to success in HP eradication and to erosion/ulcer healing.

Among the patients there were no pregnant or breast-feeding women or patients with oncological, severe internal, infectious, or psychiatric diseases. All patients were informed about the UGIE examination and the associated risks and gave their written consent. Statistical analyses were conducted with the use of Statistica software (version 10; StatSoft Inc., Chicago, IL, USA).

Results

HP was observed in 26 (72.2%) of the 36 patients on UGIE; 18 patients (50%) presented with erosions, 14 of whom were also HP positive. Four patients (11.1%) had erosions/ulcers without any presence of HP, and 6 patients (19.4%) did not present with either (Table 4).

Among the HP-positive/erosion/ulcer-positive patients, eradication therapy was fully successful (UAS7 score = 0) in 6 patients (42.9%) and partly successful (UAS7 score ≤6) in 7 patients (50%). Of the 4 patients erosion/ulcer-positive on UGIE-1, 2 patients were erosion/ulcer-negative on UGIE-2. The results of the eradication therapy and their association with the disease symptoms are shown in Table 1.

Remission of urticaria was achieved in 15 patients (41.7%). Relating the CSU remission data to HP eradication and erosion/ulcer healing showed a weak association

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Table 1. Results of the first and second gastroscopy and *Helicobacter pylori* testing of the 36 patients with chronic spontaneous urticaria

Patient No.	First gastroscopy		Second gastroscopy		Remission of urticaria
	H. pylori positive	erosion/ulcer positive	*H. pylori* positive	erosion/ulcer positive	
1	Yes	Yes	No	No	Yes
2	Yes	Yes	No	No	Yes
3	Yes	Yes	Yes	No	Yes
4	Yes	Yes	No	Yes	No
5	Yes	Yes	Yes	No	Yes
6	Yes	Yes	No	Yes	No
7	Yes	Yes	Yes	Yes	No
8	Yes	Yes	No	No	Yes
9	Yes	Yes	No	No	Yes
10	Yes	Yes	No	No	Yes
11	Yes	Yes	No	Yes	No
12	Yes	Yes	Yes	No	Yes
13	No	Yes	No	Yes	No
14	No	Yes	No	Yes	No
15	No	Yes	No	No	Yes
16	Yes	No	No	No	No
17	Yes	No	No	No	No
18	Yes	No	No	No	No
19	Yes	No	No	No	No
20	Yes	No	No	No	No
21	Yes	No	No	No	No
22	Yes	No	No	No	No
23	Yes	No	No	Yes	Yes
24	Yes	No	Yes	No	No
25	Yes	No	No	No	No
26	Yes	No	No	No	No
27	No	No	Not done	Not done	No
28	No	No	Not done	Not done	No
29	No	No	Not done	Not done	No
30	No	No	Not done	Not done	Yes
31	No	No	Not done	Not done	Yes
32	No	Yes	No	No	Yes
33	Yes	Yes	No	No	Yes
34	Yes	No	No	No	No
35	Yes	Yes	No	Yes	No
36	No	No	Not done	Not done	Yes

The second gastroscopy was only performed on those with pathological findings on the first gastroscopy or with *H. pylori*-positive findings.

with HP eradication (Table 2) but a strong association with erosion/ulcer healing (Table 3).

There was no significant difference in gastric erosion/ulcer prevalence between the HP-positive and the HP-negative group (Table 4).

Discussion

Compared with the prevalence of gastric erosions in 1,311 controls who underwent gastroscopy for routine cancer screening (6.8%) [14], the results of the present study show a significantly higher rate of gastric erosions

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Table 2. Eradication results of the HP-positive patients undergoing UGIE-2 (n = 26)

	Remission of CSU was achieved, n (patient No.)	No remission, n (patient No.)
Eradication succeeded	7 (1, 2, 8–10, 23, 33)	14 (4, 6, 11, 16–22, 25, 26, 34, 35)
Eradication failed	3 (3, 5, 12)	2 (7, 24)

HP, *Helicobacter pylori*; CSU, chronic spontaneous urticaria; UGIE-2, second upper gastrointestinal endoscopy. Fisher exact test, one-tailed: $p = 0.27$; two-tailed: $p = 0.34$.

Table 3. 2 × 2 table for the assessment of statistical significance of healing erosions (n = 19[a] cases)

	Remission of CSU was achieved, n (patient No.)	No remission, n (patient No.)
Patients with healed erosions	11 (1–3, 5, 8–10, 12, 15, 32, 33)	0
Patients with unhealed erosions	1 (23[a])	7 (4, 6, 7, 11, 13, 14, 35)

CSU, chronic spontaneous urticaria; UGIE-1/2, first/second upper gastrointestinal endoscopy. Fisher exact test, one-tailed: $p = 0.0002$; two-tailed: $p = 0.0002$. [a] In patient 23, erosions had not been seen on UGIE-1, but had appeared on UGIE-2 after eradication (although remission had been achieved).

in CSU patients (41.7%). At 72%, the prevalence of HP infection, however, does reflect the HP infection rate in Moscow, which some studies state to be as high as 90% [15].

The findings of this study indicate that gastric erosions/ulcers play a role in urticaria pathogenesis independently of HP infection. The limitation of the study is that a double-blind clinical trial design with placebo-controlled eradication therapy is missing, and that the study was performed in a longitudinal routine setting. However, this limitation can also be regarded as a strength, since it was not the primary question to investigate the efficacy of eradication therapy but the role of gastric erosions/ulcers in the pathogenesis of CSU, which can only be detected by gastroscopy; thus, in some way the patient remains blinded. The results of this study show that routine treatment of gastric erosions/ulcers is beneficial in CSU, and that gastric erosions/ulcers appear to be involved in triggering CSU independently of their etiology.

HP diagnosis and eradication is part of the extended diagnostic program for patients with CSU according to the guidelines [1], and since HP infection has been reported as a causative factor for urticaria, and certainly also independently of urticaria, treatment of gastric erosions/ulcers should be aimed for. However, since the success of eradication therapy may be influenced by several factors (e.g., adherence to nicotine abstinence [16 and others]) and erosions/ulcers may persist in spite of HP having been eradicated, complete healing of the underlying gastrointestinal inflammatory process may be required for urticaria symptom relief, as our results suggest. Thus, in patients not responding with a reduction in UAS7 score after eradication therapy, follow-up gastroscopy is required to check for persisting gastric erosions/ulcers. An important further aspect to mention is that recurrence of gastric erosions/ulcers can occur. This should be remembered with regard to patients with flare-ups of urticaria. Cases in which renewed HP infection triggered CSU symptoms were previously observed among patients to whom eradication therapy was prescribed [17]. Gastric erosions/ulcers are pathognomonic of severe gastric inflammation. This study, however, raises the question whether also subclinical inflammation without erosions (e.g., in patients with acid reflux) contributes to the development and perpetuation of urticaria.

Patients often link cases of flare-up in CSU to stress, but good studies are missing [as reviewed in 18]. As gastrointestinal mucous inflammation may fluctuate and can be triggered or worsened by factors like stress, this might be an explanation, but it remains speculative until further studies in this area will have been performed.

Table 4. Upper gastrointestinal erosions/ulcers on UGIE-1 in HP+ and HP– groups (n = 36 cases)

	EU+	EU–
HP+	14	12
HP–	4	6

UGIE-1, first upper gastrointestinal endoscopy; HP, *Helicobacter pylori*; EU, erosion/ulcer. Fisher exact test, one-tailed: $p = 0.36$; two-tailed: $p = 0.71$.

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The mechanism by which patients with HP and gastritis develop urticarial symptoms is not known yet [19]. Many consider HP infection itself the culprit; the majority of studies conclude that the HP antigen stimulates autoimmune reactions and eradication therapy has therefore a causal effect on urticarial symptoms, but that in eradicating HP there always also is a positive effect on the gastritis [19–21]. Our findings indicate that possibly the gastric inflammation itself is the cause. A potential pathomechanism would be an increased histamine level caused by degranulation of the stomach mast cells, which occurs in gastritis or peptic ulcers [22]. This induces an increase in hydrochloric acid synthesis by parietal cells, an effect that can also be triggered by the consumption of spicy, greasy, or acidic food, by alcohol, or by medications such as acetylsalicylic acid, as well as by duodenogastric bile reflux in gastritis patients [23–25]. It is established that gastric inflammation leads to increased permeability of the gastric mucous membrane [26].

In CSU related to pseudoallergy to food, it was shown that this is associated with altered gastroduodenal permeability and that urticaria subsides if permeability is restored [27]. However, the mechanism – whether food ingredients better permeate the impaired mucosa or whether this is associated with gastric histamine release – remains unclear. Increased histamine concentrations in the blood of patients with spontaneous urticaria (from 11.38 ± 11.67 to 12.43 ± 7.97 nM) compared to healthy subjects (8.75 ± 2.55 nM) have been observed, although the reason for this is unclear [22]. However, an increased histamine concentration of 12.43 nM (range 4.67–29.86) was observed in an experiment with the gastric secretion stimulant pentagastrin [28]. Whether these increases in blood histamine are sufficient to provoke systemic urticaria remains unclear but should be further investigated as a potential mechanism linking gastric inflammation with urticaria.

In conclusion, while the mechanism of how gastric ulcers induce urticaria still needs further investigation, this study shows that apparently inflammation of the gastric mucosa is a very relevant factor independently of HP infection, and should therefore be treated if observed. This has implications for the relevance of gastroscopy in the workup of CSU.

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Statement of Ethics

The study was approved by the Local Ethics Committee of Moscow City Clinical Hospital No. 7.

Disclosure Statement

The authors declare no conflict of interest.

Author Contributions

S. Zheleznov: design of the study, patient recruitment and clinical evaluation, and writing of the manuscript; T. Zuberbier: design of the study and writing of the manuscript; G. Urzhumtseva, N. Petrova, Z. Sarsaniia, and N. Didkovskii: patient evaluation and gastroscopic evaluation; T. Dörr: writing and critical revision of the manuscript.

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