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HELICOBACTER PYLORI AND CHRONIC URTICARIA: IS THERE A CAUSE-CONSEQUENCE RELATIONSHIP?

HELICOBACTER PYLORI I HRONIČNA URTIKARIJA: POSTOJI LI UZROČNO-POSLEDIČNA VEZA?

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Apstrakt

Hronična idiopatska urtikarija (HIU) se definiše skoro svakodnevnom pojavom urtika u trajanju od najmanje 6 nedelja, pri čemu uzrok ostaje neotkriven. Evropska Akademija za Alergologiju i Kliničku Imunologiju ne odvaja HIU od hronične urtikarije (HU) s obzirom na postojanje velikog broja različitih uzroka koji mogu izazvati HU. Hronične aktuelne ali i latentne infekcije se navode kao jedan od najčešćih faktora koji pokreću HU. U oko 70% slučajeva, sanacijom infekcije dolazi do nestanka HU. U literaturi su podaci dosta šaroliki, čak kontroverzni, kada je uzročnik infekcije u pitanju. Objavljena je studija u kojoj je infekcija izazvana sa Helicobacter pylori u obliku gastritisa bila prisutna kod 60% osoba sa HU koje su imale infekciju.
Infekcija izazvana Gram-negativnom bakterijom Helicobacter pylori (Hp) je jedna od najčešćih infekcija i smatra se da je više od polovine ukupne svetske populacije inficirano. Kliničke manifestacije su različite i zavise kako od osobina uzročnika tako i od genetske predispozicije inficirane osobe.
Iako se prevalencija (Hp) inficiranih među obolelim od HU (24-70.58%) značajno ne razlikuje od prevalencije među inficiranim bez HU, dokazano je da ona može izazvati HU kod oko trećine predisponiranih osoba.
Da Hp infekcija nije okultna infekcija u HU govori podatak da je u jednoj seriji obolelih od HU izazvala simptome gastritisa kod svih inficiranih. Preporuka o potrebi eradikacije Hp infekcije kod oboleli od HU mora biti zasnovana na činjenicama. Utvrđeno je da su šanse za izlečenje HU statistički značajno veće kod onih osoba kod kojih je Hp infekcija uspešno sanirana. Lečenje ovih osoba antibioticima treba da se sprovede, ali pri tome treba tragati i lečiti i druge uzroke koji mogu biti istovremeno prisutni. Treba znati da će lečenje samo aktivne infekcije dovesti u oko trećine lečenih do nestajanja HU. Recidive infekcije treba pravovremeno otkriti i lečiti.
Može se zaključiti da infekcija izazvana sa Helicobacter pylori može pokrenuti hroničnu urtikariju i da svaku osobu kod koje je utvrđena aktivna infekcija treba uputiti gastroenterologu. U daljem timskom radu blagovremeno otkrivanje i lečenje recidiva infekcije predstavlja postulat.

Ključne reči
Hronična urtikarija, Infekcija, Helicobacter pylori

Key words
Chronic urticaria, Infection, Helicobacter pylori

CHRONIC URTICARIA

Urticaria represents a heterogeneous group of diseases/disorders/conditions with a distinct transitory vascular skin reaction, the development of urticarial lesions: wheals and/or angioedema. Chronic urticaria (CU) is defined as a frequent or daily occurrence of hives persisting for more than 6 weeks (1). In the majority of cases, a cause cannot be individuated. This entity has been suggested to be named as chronic ordinary urticaria (COU) (2).

Chronic urticaria is a 6-week or longer history of daily or almost daily itchy cutaneous wheals with individual lesions lasting less than 24 hours. It is defined ”idiopathic” if no physical, allergic, infectious, drug-related or vasculitic cause can be identified (3). Chronic idiopathic urticaria (CIU) is defined by the almost daily presence of urticaria for at least 6 weeks without an identifiable cause. Symptoms include short-lived wheals, itching and erythema.

Autoimmune chronic urticaria is emerging as a dominant cause of CU, potentially explaining up to 60% of previously idiopathic cases. CU impedes significantly a patient’s quality of life. It is an extremely distressing condition for the patient. A recent study has reported that the degree of personal, social and occupational disability is similar to that of patients with awaiting surgery for severe coronary artery disease.

Approximately 1-25% of the population will experience at least one episode of urticaria in their lifetime, while one fourth of these people will develop chronic uricaria (4). Chronic idiopathic urticaria (CIU) affects between 0.1% and 3% of the United States and Europe population. CIU is characterized by the spontaneous appearance of widespread edematous pruritic wheals that are surrounded by a bright red flare: the condition lasts 6 weeks and is often recurrent.

According to Champion, chronic urticaria is a skin disorder characterized by recurrent, transitory, itchy wheals, which occur daily or almost daily (two or more times per week) for at least three months. One-half of the patients demonstrate wheals beyond 6 months but one-fifth of patients persist with considerable disability and reduction of quality of life beyond 10 years (5). In the case of coexisting angioedema, 75% of the patients will develop CU for

Table 1. PRECIPITATING FACTORS IN CHRONIC URTICARIA (n=79)*

CHRONIC URTICARIA	PHYSICAL n=10(13.7%)		MEDICAMENT n=35 (47.9%)		CONTACT n=11(15.1%)		IDIOPATHIC n=17 (23.0%)		TOTAL n=73(100.0%)	
	n	%	n	%	n	%	n	%	n	%
ATOPY	1	10.0	0	0.0	0	0.0	3	17.6	4	5.5
ANGIOEDEMA	0	0.0	15	42.9	7	63.6	9	52.9	31	42.5
FOCAL INFECTIONS	1	10.0	12	34.3	0	0.0	2	11.8	15	20.5
EMOTIONAL	4	40.0	3	8.6	0	0.0	1	5.8	8	11.0
CANDIDA (intestinal)	1	10.0	1	2.9	0	0.0	2	11.8	4	5.5
PARASITES (ova in stool)	0	0.0	1	2.9	0	0.0	0	0.0	1	1.4

* Jovanović M. Contact urticaria syndrome within contact sensitization (dissertation). Novi Sad, SR: Novi Sad Univ.;1996.

more than 5 years. It is one of the most common and frustrating disease for both patients and physicians (3).

In the new guidelines from the Dermatology section of the European Academy of Allergy and Clinical Immunology (EAACI) and the Global Allergy and Asthma European Network (GA2LEN), urticaria is defined as the rapid appearance of wheals with or without angioedema, whereas chronic urticaria (CU) is defined as urticaria that lasts 6 weeks. It is characterized as the daily or almost daily occurrence of wheals that lasts more than 6 weeks. The wheal represents oedema of the upper and mid-dermis. The affected skin exhibits up regulation of vascular adhesion molecules and a mixed inflammatory perivascular infiltrate of variable intensity (1).

The EAACI/ GA2LEN guidelines do not differentiate between CU and CIU, since multiple causes of CU exist, and a sizeable proportion of cases previously considered as idiopathic origin have been shown to involve autoantibodies against the IgE and /or the α-chain of the high-affinity IgE receptor for binding immunoglobulin class E (FcεRIα) (4).

up to 50% in 6 months (5,7). Secondly, regarding eliciting factors of CU, different results obtained by different authors may reflect true differences between populations. Moreover, the presence of positive autologous serum skin test (ASST) is not diagnosic but only suggestive of an autoimmune origin (1). Thus, the relation between different pathomechanisms and autoimmunity requires further investigations (8).

PRECIPITATING FACTORS IN CHRONIC URTICARIA

A variety of potential causative factors has been implicated in the pathogenesis of individual cases, such as infections, food additives, medications, malignancy, physical factors and autoimmune diseases. Literature data have shown different results (Tables 1-3) (9-11).

Thus, Wedi et al. provided very interesting data, with a very high prevalence of potential focal infections. In their study 43% of patients presented important focal infections (Table 3) (10).

Table 2. PRECIPITATING FACTORS IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA (n=17)*

PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA		n	AE
PATIENTS WITHOUT PRECIPITATING FACTORS		7	1+1**=2
PATIENTS WITH PRECIPITATING FACTORS	ATOPY	3	2
	AEROALLERGENS	3	3
	AUTOIMMUNE DISEASES: SYSTEMIC LUPUS ERYTHEMATOUS	2	1
	POLYGLANDULAR AUTOIMMUNE SYNDROME	1	1
	MALIGNANT DISEASE: CARCINOMA OF THE LUNG	1	0
TOTAL		17	9

n, number of patients; AE, angioedema; **hereditary angioedema.

*Jovanović M. Contact urticaria syndrome within contact sensitization (dissertation). Novi Sad, SR: Novi Sad Univ.;1996.

PHISIOPATHOLOGY OF CHRONIC URTICARIA

The physiopathology of CU is based on the cutaneous mast cell release of mediators, mainly histamine. An autoimmune mechanism is suggested in more than a half of all patients with CIU since the intradermal injection of autologous serum produces an urticarial response by activating normal donor mast cells and basophils with histamine release (2). In most cases this autologous serum skin test (ASST) which is reasonably sensitive and specific marker of histamine-releasing activity on basophils, is positive due to the circulating autoantibodies against IgE receptors of mast cells and basophils or/and against IgE. Although the pathomechanism involved in remaining ASST-positive patients is still unknown, it is believed that mast cell degranulation initiates the inflammatory cascade in autoimmune CU (6).

However, 2 major points has to be taken into account. Firstly, the natural course of CU shows a high rate of spontaneous healing

INFECTIONS

Overt or hidden bacterial, viral, fungal as well as protozoan infections have been reported among the most frequent possible triggering factors in the development of chronic urticaria (Table 4) (7,9,10,12,13). Moreover, Wedi et al. reported a strikingly high prevalence of Helicobacter pylori gastritis, which accounted for 60% of all focal infections in their study (Table 4) (9). In contrast, other focal infections were less frequent. Among patients with focal infections other than Helicobacter pylori, after treatment of the focal infection, 70% showed healing of CU (9).

HELICOBACTER PYLORI INFECTION

At the present, Helicobacter pylori (Hp) infection is probably the most common chronic bacterial infection in humans, affecting more than a half of the world population. It represents the main cause of gastroduodenal ulcer disease, plays an etiologic role in the

Table 3. POSSIBLE ELICITING FACTORS OF CHRONIC URTICARIA BASED ON PATIENT'S HISTORY AND EXTENSIVE DIAGNOSTIC APPROACH (n=100)*

ELICITING FACTOR	%
FOCAL INFECTION	43%
PSEUDOALLERGIC REACTIONS	15%
ANTIBODIES TO THYROID	5%
MALIGNANT DISEASE	2%
IDIOPATHIC ORIGIN	35%
TOTAL	100%

*,Wedi B, et al. Int Arch Allergy Immunology 1998;6:288-94.

development of chronic active gastritis, gastric carcinogenesis and low-grade gastric mucosa-associated lymphoid tissue lymphoma. The prevalence is high especially in the developing world (14,15).

The heterogeneous clinical presentation of the infection which depends on different interactions between Hp strains and host genetic differences as well as recent findings, suggest an association with some extraintestinal diseases ranging from rosacea to scleroderma (16,17). The role of Hp infection in the pathogenesis of chronic UC has been assessed for more than 18 years. Most recently, the possible role of Hp as a triggering factor for at least some cases of CIU has become the reality (18-24).

By producing inflammation in gastrointestinal tract, Hp can facilitate absorption of antigens or unmask existing antigens (25). Once this occurs, the production of IgE antibodies responsible for urticarial symptoms might continue even after eradication of symptoms (25). Thus, HP infection may perpetuate the urticarial tendency of an infected person.

COLONIZATION AND MUCOSAL INFLAMMATION

Helicobacter pylori is a Gram-negative spiral microaerophilic bacterium which can infect gastric mucosa. Hp was shown to have a toxic effect on the mucosa cells, where the pathogen is able to induce interleukin 8 (IL-8) mRNA expression. Furthermore, IL-8 as well as urease and lipopolysaccharide, both secreted by Hp, may induce attraction of neutrophilic granulocites, which are able to destroy the mucosa barrier via oxidative stress and proteolytic enzymes. Penetration of food allergens/pseudoallergens may be promoted by this toxic cell damage. This hypothesis is supported by the fact that Hp infection is not an occult infection in patients with CU; it led to symptoms of chronic gastritis in all patients in one series (13).

CUTANEOUS PATHOLOGY

Regarding structural components (flagella, adhesions, membrane lipopolyssacharides) or products of Hp (urease, protease, phospholipase, cytotoxin), several relationships between Hp colonization and mucosal inflammation have to be discussed. Generally, Hp may cause immunomodulation in infected persons, which may also involve the skin. Different strains of Hp may elicit different pathogenetic responses, depending not only on the virulence of Hp (e.g., type I bacteria express the vacuolating cytotoxin Vac A and the cytotoxin-associated gen Cag A and are recognized to be more virulent producing a more severe inflammatory response), but also on the diverse host and environmental factors (26,27,28). Recently a modulatory action of Hp on histamine release from mast cells and basophils was demonstrated in vitro (29).

The other possibility is that Hp may induce some unknown IgE-mediated or non-IgE-mediated immunomechanism, which leads to urticarial disease. Experimental evidence supporting this concept demonstrated the presence of specific IgE detected against Hp on basophils and in sera (30).

When IgA-, IgG-, and IgE-mediated immune response against Hp antigens were analyzed, some bacterial immunoresponsive proteins were identified in cases of CU (16).

Immuno-blot analysis identified a specific serum IgG and IgA response to a 19-kDa outer membrane protein Hp-associated lipoprotein 20 (lpp20) in Hp-positive patients. The prevalence of anti Hp-associated lpp20 antibodies was significantly higher in Hp-positive patients with urticaria than in patients with severe Hp-associated gastritis without urticaria (21). This phenomenon may lie in the protective effect of anti-lpp20 IgG antibodies since the 19-kDa lpp20 may act as a protective antigen. This protective antibody response may have a functional role in prevention or mitigation of gastritis associated with Hp infection. However, the protection depends on the magnitude and subclass of the response; for example, an IgG1 subclass monoclonal antibody raised against Hp lpp20 can reduce or even prevent Hp colonization (31). Patients with CU who exhibited the high level of anti-lpp 20 had no dyspeptic symptoms in their history and only a mild gastritis that was seen on endoscopy (21). On the other hand, people may develop a severe gastritis with overt dyspeptic symptoms if harboring Hp with zero or low levels of anti-lpp20 as it has been detected in the selected dyspeptic control group (21). Thus, in addition to their putative gastroprotective effect, IgG and partly IgA antibodies against Hp associated lpp-20 could act as a source of autoimmunity, via cross reactivity between the bacterial lpp20 and some skin antigen components (21). The anti- FcεRIα antibodies in chronic urticaria are related predominantly to the complement fixing subtypes IgG1 and IgG3. In this context, there is growing evidence that the phenomenon of parasite-host mimicry may initiate or maintain autoimmunity. A great number of cross-reacting (auto) antibodies may interact with the stomach and duodenal alterations caused by Hp.

Table 4. FOCAL INFCTIONS AS POSSIBLE ELICITING FACTORS OF CHRONIC URTICARIA*

FOCAL INFECTION	%
HELICOBACTER PYLORI GASTRITIS	60%
EAR-NOSE-THROAT FOCUS	21%
EPSTEIN-BARR VIRUS, CYTOMEGALOVIRUS	9%
DENTAL	5%
YERSINIOSIS	5%
TOTAL	100%

*,Wedi B, et. Int Arch Allergy Immunology 1998;6:288-94.

One-third of patients with CU have circulating functional antibodies against the high-affinity IgE receptors FcαRI, or IgE, and this forms the basis for a positive autologous serum skin test. The prevalence of positive ASST in patients with CU and Hp infection is significantly higher than in patients with CU but without Hp infection (8), indicating that the presence of Hp might predispose to the development of other associated autoimmune phenomena (8). Many drug-induced autoimmune diseases continue to progress even after drug withdrawal (e.g., pemphigus). Once induced or triggered by a drug, the biological behavior and course of the disease do not differ from those of an idiopathic disease (8).

Thyroid autoimmunity has been considered an important factor in the pathogenesis of CU in Hp-infected patients. In cases of CU with and without thyroid autoimmunity, a different prevalence of Hp infection was found and the thyroid autoimmunity was connected with CagA (+) Hp strains (27). A higher prevalence of antithyroid antibodies was found in patients with CU and positive ASST, then in patients with CU and negative ASST. Whether these antibodies have any pathogenetic role in the development of CU in Hp-infected patients is questionable, as antithyroid antibodies usually persist even after urticaria disappeared (32,33). Similarly, a higher prevalence of Hp-specific antibodies was found in patients with CU and positive ASST, then in patients with CU and negative ASST (8). Magen et al. showed that eradication of Hp infection sig-

nificantly and equally improved CU in patients with and without positive ASST (33). The presence of a positive ASST response does not seem to be a predictor for a good clinical response to antihistamine therapy as well (34). The results of these studies do not support the hypothesis that in patients with CU, clinically recognized autoimmunity (by ASST and plasma antithyroid antibodies) may be a factor which can modify Hp-induced immunomodulation, but other yet unknown aspects of Hp to cause some kind of immune deviation in CU (7,33). Moreover, much more work needs to be done before the ASST is accepted as a valuable tool for the classification of autoimmune urticaria (35,36).

PREVALENCE OF HELICOBACTER PYLORI ASSOCIATED GASTRITIS IN CHRONIC URTICARIA

Based on our current knowledge, the prevalence of Hp infection in patients with CU (24-70,58%) does not significantly differ from that in patients without CU (25-84%) (12-14, 28,37). Thus, Dauden et al. found the high prevalence of 68% in patients with CU, which did not differ from the prevalence of 84% estimated in the general population in the same geographic area (37). In a double blind, placebo-controlled, crossover study, only 24% of patients with CIU had an active Hp infection which correlated with the prevalence of a comparable age population but without urticaria in Switzerland (19% asymptomatic people, 39% in dyspeptic people) (12). In one Finish report, 25% of the patients with CU were positive for Hp. The prevalence of Hp infection was not significantly higher among urticaria patients compared with the normal Finish population in any of the age groups studied. The prevalence rose with age similarly to that of the control subjects (38). The high prevalence of Hp infection has been reported from India. The prevalence of 70.58% among patients with CU did not differ from the prevalence of 67.64 % found in the control group without CU (14).

Table 5. THE EFFECT OF ANTIBIOTIC THERAPY FOR HELICOBACTER PYLORI-INFECTED PATIENTS WITH CHRONIC URTICARIA*

PATIENTS WITH CHRONIC URTICARIA			COMPLETE REMISSION OF URTICARIA				
n	AGE (years)	FOLLOW-UP (months)	HP (+) TREATED ERADICATED	HP(+) TREATED NOT ERADICATED	HP(+) NOT OR PLACEBO TREATED	ALL HP(+) NOT ERADICATED	HP(-) CONTROL
266	10-82	1.5-9	59/191 (30.9%)	7/38 (18.42%)	11/45 (24.4 %)	18/83 (21.7%)	10/74 (13.5%)

HP, Helicobacter pylori; n, number of treated patients with chronic urticaria Helicobacter pylori infection completing study
*, Federman DG, et al. J Am Acad Dermatol 2003;49:891-4.

Contrary to the data regarding active Hp infection, the Hp serology studies revealed (almost always) the significantly higher prevalence in patients with CU than in those without CU (7,8,13). In one study from Germany, the circulating specific IgG-antibodies against Hp were detected in all patients with CU, and in 78% of patients without CU (13). In a European Mediterranean population-based study on the prevalence of anti-Hp serology, anti Hp antibodies were present in 51% of the study population (39).

Nevertheless, the assessment of Hp-specific IgG and IgA antibodies (the sensitivity and specificity of the enzyme-linked immunosorbent assay-ELISA for IgA is 88.9% and 97.1%, respectively, and for IgG 96.7% and 95.5%, respectively) cannot be used for the detection and establishment of Hp infection. Since these antibodies are associated with active gastritis in only some patients, the assessment of antibodies does not indicate active disease and titers may remain positive even after successful eradication therapy. All patients should be examined for Hp infection actively, by the urea breath test (^{13}C-UBT) and/or upper endoscopy with antral biopsy for urease test and histopathology (to confirm Hp). Patients infected with Hp (diagnosed by the ^{13}C-UBT, and/or endoscopy with rapid urease test or histology or both), should receive eradication therapy. The response to eradication therapy should be evaluated by the ^{13}C-UBT or the monoclonal fecal antigen assay which has the sensitivity of 94% and specificity of 100% (40). The histology for the diagnosis of Hp infection has the sensitivity and specificity between 53-90%; the specificity of the rapid urease test varies from 95-100%, while the sensitivity varies from 85-95%. The sensitivity of the ^{13}C-UBT ranges from 95-97% (41).

Regarding clinical presentation of CU, no significant differences between Hp-infected and non-infected patients with CU were noticed for duration of the disease, age and sex distribution, prevalence of angioedema, other focal infections or atopy (7,13,15,20).

As we all know, all patients with CU should undergo an extensive diagnostic work-up including history, clinical and laboratory examinations (7,21). In addition, every more extensive (invasive) investigation for focus of infection in other location is mostly performed when indicated by the patient's history (28,34). However, gastric complaints were reported by only 27% of patients with Hp gastritis and CU (10,15). The prevalence did not differ from the prevalence of 28 % found in the control group without CU (15). However, only 37% of asymptomatic adults were shown to have an Hp-associated gastritis (42), whereas Hp was detected in 96% of patients with CU who underwent gastroscopy (10). Moreover, Hp infection was not always an occult infection in patients with CU; it led to symptoms of chronic gastritis in all patients in one series (13). Furthermore, patients with CU who exhibited the high level of antibodies against Hp associated lpp-20 lipoprotein had no dyspeptic symptoms in their history and only a mild gastritis that was seen on endoscopy (21). Selection of patients may probably be the main reason for these differences.

Generally, Hp infection is frequent, but we should bear in mind that regardless to its prevalence, it would trigger urticaria only in some (somehow predisposed) infected patients.

EFFECT OF ANTIBIOTIC THERAPY FOR HELICOBACTER PYLORI - INFECTED PATIENTS WITH CHRONIC URTICARIA

Recommendations to administrate antibiotic treatment for Hp infection in patients with CU should be evidence-based. The reported association between Hp and CU is consistent with a triggering effect of Hp but does not provide strong evidence for a causal relation between Hp-associated gastritis and CU. Results on the effects of Hp eradication on the course of ICU are conflicting. Eradication of Hp infection was achived in 27-96% (12,14) and in 8-81.2% was the eradication associated with the resolution of urticaria (14,18,37). Though representing a potential subject for meta-analysis, available reports still differ in substantive ways. As

far as we know, there is only a systemic review (published in English), on the effect of antibiotic eradication of Hp on urticarial improvement (23). Included studies met the following criteria: 1) patients had to experience urticaria for at least 6 weeks; 2) other known causes of urticaria were excluded; 3) the initial diagnosis of Hp infection was made by either serology, urea breath test, or by upper endoscopy; 4) an acceptable course of an antibiotic with known activity against Hp was conducted. The therapy varied among the different studies. Antibiotics (amoxicillin, clarithromycin or tetracycline) and metronidazole were given from 7-14 days, proton pump inhibitors (omeprazole, lansoprazole) were given concurrently for 7-28 days. There was a great variability in time of follow-up evaluation (Table 5) (23). Two analyses were performed, eradication versus unsuccessful eradication or placebo treatment, and eradication versus control persons who were not Hp-infected. It was shown that eradication of Hp was significantly associated with remission of urticaria, with an odds ratio 2.9 (95% confidence interval 1.4-6.8;P=0.005). When patients with eradication of Hp were compared with control persons who were not Hp-infected, the odds ratio for remission of urticaria was 4.7 (95% confidence interval 2.6-17.6), p<0.001) (23).

Patients with CU and Hp infection should receive the therapy for eradication of Hp. However, other possible causes of the disease should be sought and treated. For example, in 45% of Hp-infected and in 68% of non-infected patients with CU other focal infections were found, however there was no significant difference between the 2 groups (13). Furthermore, in a recent study, Helmig, et al. found at least one additional focus in 81% of Hp-infected patients with CU (Table 6) (7). In one case control study, patients who were not Hp-infected, reached a comparable clearance rate of Hp-infected patients if antimicrobial therapy for intestinal candidiasis or sinusitis was successful, or diet free from nutritional and/or drug-related provocation factors was conducted (13).

Table 6. COEXISTING FOCAL INFECTIONS IN HELICOBACTER PYLORI-INFECTED PATIENTS WITH CHRONIC URTICARIA (n=74)*

PATIENTS WITH COEXISTING FOCI	n	%
EAR-NOSE-THROAT AND TEETH FOCUS	25	33.8
PASS THROUGH VIRAL HEPATITIS	11	14.8
YERSINIOSIS	31	41.9
OTHER FOCI	20	27.0
TOTAL	60	81.1

CU, chronic urticaria; HP, Helicobacter pylori; n, number of patients
*, Helmig S, et al. Helicobacter 2008;13:341-5.

Looking at these data, some facts have to be taken into account. Firstly, after successful eradication of infection with antibiotics, only one third of patients with Hp-associated CU will be in remission. Secondly, only patients who have active infection will benefit in resolution of urticaria. Thirdly, the majority of patients with the active infection will concurrently have causes unrelated to Hp.

CONCLUSION

At the present, it can be concluded that the reported association between Hp and CU is consistent with a triggering role of Hp. Every patient with CIU should be sent to a gastroenterologist. It should be kept in mind that recurrence shortly after successful therapy may be the main reason for the recurrence of urticaria.

Abstract

Chronic idiopathic urticaria (CIU) is defined by the almost daily presence of urticaria for at least 6 weeks, without an identifiable cause. The European Academy of Allergy and Clinical Immunology (EAACI) and the Global Allergy and Asthma European Network (GA2LEN) guidelines do not differentiate between chronic urticaria (CU) and CIU, since multiple causes of CU exist. Overt or hidden bacterial, viral, fungal and protozoan infections have been reported as the most frequently recognized triggering factors. A strikingly high prevalence of Helicobacter pylori gastritis accounted for 60% of all focal infections, was reported. Of the patients with focal infections other than Helicobacter pylori, 70% showed healing of CU after treatment of the focal infection.
Helicobacter pylori (Hp) infection affects more than a half of the world population. The heterogeneous clinical presentation which depends on different interactions between Hp strains and host genetic differences, suggests an association with some extraintestinal diseases ranging from rosacea to scleroderma. Most recently, the possible role of Hp as a triggering factor for at least some cases of CIU has become the reality. It seems that the prevalence of Hp infection in patients with CU (24-70,58%) does not significantly differ from that in patients without CU (25-84%). Generally, Hp infection is frequent, but regardless to its prevalence, it will probably trigger urticaria only in some (somehow predisposed) infected patients.
Hp infection was not always an occult infection in patients with CU; it led to the symptoms of chronic gastritis in all patients in one series. Recommendations to administrate antibiotic treatment for Hp infection in patients with CU should be evidence-based. It was found that resolution of urticaria was more likely when antibiotic therapy was successful in eradication of Hp. Patients with CU and Hp infection should receive the therapy for eradication of Hp, however, other possible causes of the disease should be sought and treated. After successful eradication of infection, only one third of patients with H-associated CU will be in remission; only patients who have active infection will result in resolution of urticaria; the majority of patients with the active infection will have causes unrelated to Hp.
At the present, it can be concluded that the reported association between Hp and CU is consistent with a triggering role of Hp. Every patient with CIU should be sent to a gastroenterologist. It should be kept in mind that recurrence shortly after successful therapy may be the main reason for the recurrence of urticaria.

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ABBREVIATIONS:

CU- Chronic urticaria
COU - Chronic ordinary urticaria
CIU - Chronic idiopathic urticaria
EAACI - European Academy of Allergy and Clinical Immunology
GA2LEN - Global Allergy and Asthma European Network
FcεRIα - Alpha chain of the high-affinity receptor for binding immunoglobulin class E
ASST - Autologous serum skin test
IgE - Immunoglobulin class E
Hp - Helicobacter pylori
IL-8 - Interleukin 8
Vac A - Vacuolating cytotoxin
Cag A - Cytotoxin-associated gen
IgA - Immunoglobulin class A
IgG - Immunoglobulin class G
lpp20 - Lipoprotein 20
ELISA - Enzyme-linked immunosorbent assay
^{13}C-UBT - Urea breath test

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