LETTER TO THE EDITOR

CHRONIC IDIOPHATIC URTICARIA AND *HELICOBACTER PYLORI*: A SPECIFIC PATTERN OF GASTRITIS AND URTICARIA REMISSION AFTER *HELICOBACTER PYLORI* ERADICATION

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Received April 13, 2011 – Accepted May 23, 2012

Chronic urticaria (CU) is defined as the occurrence of spontaneous wheals for a duration of more than 6 weeks and is the most frequent skin disease, with prevalence ranging between 15 and 25%, and is a seriously disabling condition, with social isolation and mood changes causing a significant degree of dysfunction and quality of life impairment to many patients. The main clinical features of CU are the repeated occurrence of transient eruptions of pruritic wheals or patchy erythema on the skin that last less than 24 hours and disappear without sequelae. CU is often defined as Chronic idiopathic urticaria (CIU) because the causes of CU remain unknown in the great majority (70-95%) of patients. Drugs, food, viruses, alimentary conservative substances or inhalant substances often seem to be involved in determining CIU skin flare. Despite a general agreement that bacteria infections and parasitic infestations can be involved in the pathogenesis of CIU, proven evidence of these relationships is lacking. The aim of the present study is to evaluate the prevalence of *Helicobacter pylori* (Hp) infection, and the extension and severity of gastritis in a group of CIU patients compared to controls and to evaluate the effectiveness of eradication of Hp on the CIU symptomatology, and the role of Hp infection in pathogenesis of CIU.

Helicobacter pylori (Hp), a microaerophilic gram negative bacterium, was first isolated from the human stomach by Marshall and Warren in 1983. It is an ubiquitous infection in the adult population. The prevalence among middle-aged adults is over 80% in many developing countries, as compared with 20% to 50% in industrialized countries. Mainly, the infection is acquired in infancy and is generally transmitted within families in early childhood. Hp has been demonstrated as the cause of gastritis and peptic ulcer and as being associated to gastric cancer and mucosa-associated-lymphoma i.e. MALT lymphoma (1-3). There is evidence that Hp infection is associated with extra-digestive pathologies such as autoimmune, vascular and skin diseases. The pathogenic mechanisms involved are related to the persistent inflammatory response to Hp infection with release of immune associated substances, increase in gastric permeability and/or release of mediators acting on cutaneous sensitivity. In recent studies a possible association between Hp infection and CIU has been suggested. In fact, in some studies,

Key words: chronic urticaria, Helicobacter pylori, pangastritis, MALT lymphoma

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0394-6320 (2012)

CIU patients showed regression of cutaneous signs and symptoms after Hp eradication treatment, but information on type, extension and grade of severity of the Hp-associated gastritis in CIU patients is lacking (4-7).

The aim of the present study is to evaluate the prevalence of *Helicobacter pylori* (Hp) infection, the extension and severity of gastritis in a group of CIU patients compared to controls, and to evaluate the effectiveness of eradication of Hp on the CIU symptomatology and the role of Hp infection in pathogenesis of CIU.

MATERIALS AND METHODS

Patients

From September 2002 to December 2005, 148 CIU patients (99 F; 49 M; median age 45, range 14-79 years) were observed at the Dermatology Unit of Sant'Andrea Hospital, "Sapienza" University of Rome, Italy. Diagnostic criteria of CIU were: presence of wheals from a few millimeters to several centimeters in diameter, accompanied by redness and itching; possible association with angioedema of cutaneous and subcutaneous tissues on eyelid, lip and tongue and with symptoms lasting more than eight weeks. All patients involved in the present study underwent procedures to exclude common possible causes of CIU such as drugs, food, viruses, alimentary conservative substances, inhalants, endocrine or immune diseases, teeth or lung chronic infections. Patients were withdrawn from the study when the CIU symptoms lasted less than 8 weeks

Control subjects

One hundred and three control subjects (81 F; 22 M; median age 49, range 19-79 years) all positive for Hp infection without any past or present sign or symptoms of CIU were enrolled in the study. Inclusion criteria were the presence of dyspeptic symptoms and Hp-related gastritis proved by histology. Patients were excluded if they had one of the following conditions: peptic ulcer, atrophic body gastritis, celiac disease, endoscopic diagnosis of oesophagitis, previous Hp eradication treatment, previous or present use of gastric acid antisecretory drugs, i.e. proton pump inhibitors or H2 blockers, sideropenic anaemia. All patients included in the study gave their written informed consent and the study protocol was approved by the local ethics committee.

Study design

The design of the study is shown in Fig. 1. Specifically, 143 out of 148 CIU patients underwent a Urea breath test (UBT). All were investigated with a multi-choice questionnaire regarding their gastrointestinal symptoms. Only Hp UBT-positive CIU patients underwent an upper endoscopy with 2 antral and 2 corpus-fundus biopsies. No further investigation was carried out on CIU Hp UBT-negative patients. The eradication therapy was administered to all Hp UBT-positive patients.

Diagnostic procedures

Urea Breath Test (UBT): The breath test for Hp is a non-invasive diagnostic procedure using analysis of breath samples to determine the presence of Hp. The test is based on the presence of urease produced by the bacteria. UBT was performed after overnight fasting using an acid meal composed of 75 mg of 13C labeled urea dissolved in 200 ml of orange juice (0.1 N of citric acid). Breath samples for each patient were collected in aluminized plastic bags to determine baseline values before ingestion of the acid meal and delta over baseline (DOB) values at 15 and 30 minutes after ingestion of the meal. Breath samples were analyzed by infrared spectroscopy (IRIS, Wagner Analysen-Technik, Bremen, Germany). A DOB > 4.5% was considered positive for Hp infection, as previously described (8).

Endoscopic and histological procedures: All patients underwent gastroscopy with a video-endoscope (Olympus Optical Co., Ltd., Tokyo, Japan) under sedation with intravenous midazolam and topical pharyngeal anaesthesia with 10% lidocaine. Two biopsies were taken from the gastric antrum (within 3 cm of the pyloric ring, lesser and greater curvature) and two biopsies from the mid-body along the greater curve using biopsy forceps (Olympus, Tokyo, Japan) for conventional histopathologic examination according to a standard protocol (8). All gastric biopsies were immediately fixed in formalin and embedded in paraffin. Serial 5 μm-thick sections of gastric body mucosa, perpendicular to the mucosal surface, were stained with haematoxylin-eosin (H&E) for conventional histopathologic examination. Modified Giemsa staining for Hp was performed. The degree of gastritis was assessed according to the updated Sydney System (9). The following scores were assigned to each graded variable: 0 = absence, 1 = mild, 2 = moderate, 3 = severe degree.

Statistics: data were expressed as median (range) and mean ± SEM. The *t*-test for unpaired samples was used as appropriate. Subgroups were compared by means of Fisher's exact test. The statistical analyses were carried out using a dedicated software package (MedCalc Software, Mariakerke, Belgium, version 9.2). A two-tailed p value <0.05 was considered statistically significant.

Eradication therapy and follow-up

Bismuth regimen (tripotassium dicitrate bismuthate)

(240 mg bis in die) for 2 weeks in combination with Amoxicillin 1 gr and Metronidazole 250 mg, both taken after meals tris in die for the first seven days as previously reported (10, 11).

In cases of failure: clarithromycin instead metronidazole. All patients were informed to notify the investigators about discontinuation of the therapy and the reason for doing so. The results of therapy were assessed by urea breath test six weeks after therapy. The clinical evaluation and follow-up lasted for 6 months after treatment.

RESULTS

One hundred and forty-three out of 148 CIU patients (97 females; 46 males), median age 45 years (range 18-79) with CIU-related symptoms lasting for a median time of 12 months (range 3-264) agreed to undergo an Hp UBT. Of the 143 CIU patients, 65 (45.5%) had a negative UBT with a median DOB of 0.5% (range -2.02–.6%) and 75 (52.4%) showed a positive UBT with a median DOB of 30.8% (range 6.2–14.5%). Anagraphical and clinical characteristics of UBT-positive and UBT-negative CIU patients are shown in Table I. The only significant difference between the two groups was the median age which was younger in UBT-negative compared to positive subjects (38 *vs* 46 years; p = 0.01). Even though not statistically significant, peptic ulcer and gastric cancer familiarity, previous peptic ulcer, previous Hp treatment and dyspepsia were present in CIU UBT-positive patients. However, the CIU clinical characteristics were similar in the two groups of patients (Table I). Of the 75 CIU UBT-positive patients, 52 underwent gastroscopy with biopsies as described in Materials and Methods, 23 did not accept to undergo endoscopy and were not further analyzed. Macroscopic appearance of the gastric mucosa was normal in all patients. The histology revealed a contemporary inflammation in antrum and corpus-fundus (pangastritis) in 38 (73%) patients, whereas in 13 (25%) the inflammation was limited to the antrum. In one case, no histologic abnormality was identified and was considered as an UBT false positive case. Atrophic mucosal changes were found in 10 patients, all with pangastritis. The updated Sydney score system allowed to evaluate the grade of severity of inflammation in antrum compared to gastric corpus. Inflammatory infiltrate, activity

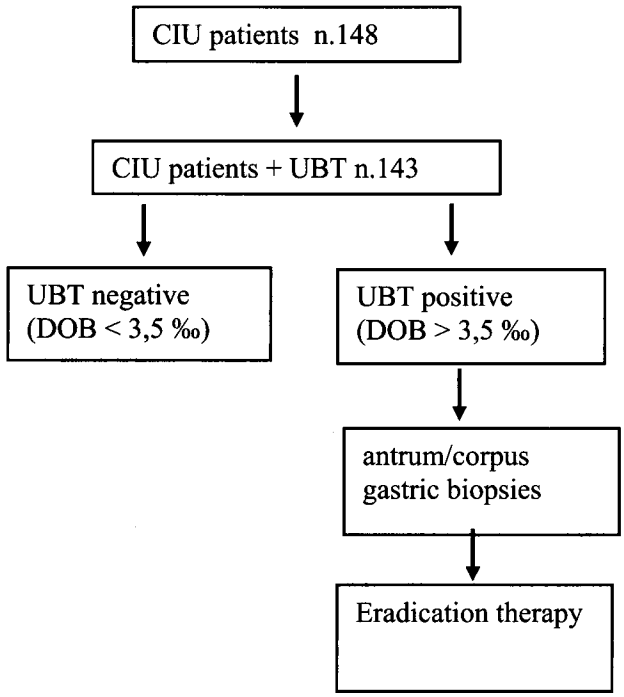

Fig. 1. *Study design: 143 out of 148 CIU patients underwent a UBT; Hp UBT-positive CIU patients underwent an upper endoscopy with 2 antral and 2 corpus-fundus biopsies; the eradication therapy was administered to all Hp UBT-positive patients.*

and atrophic changes were all significantly present in antrum compared to gastric corpus, whereas Hp density was uniformly present in all gastric mucosa (Table II, Fig. 2). The analysis of the topographical distribution of gastritis in CIU patients compared to control dyspeptic Hp-positive control group showed a greater presence of gastric inflammation localized both in antrum and corpus gastric mucosa in CIU patients than in controls (73% *vs* 42.7%; p< 0.001). However, in dyspeptic Hp-positive controls the gastric inflammation was localized only in the antrum in a significant number of cases compared to CIU patients (56% *vs* 25%; p< 0.001).

Ultimately, of the 75 Hp-positive patients treated for Hp eradication: 38 patients (50.66%) showed complete regression of urticaria symptoms; 17 patients (22.66%) showed marked improvement: mild itching, slight dermographism, sporadic wheals; 20 patients (26.66%) showed no improvement.

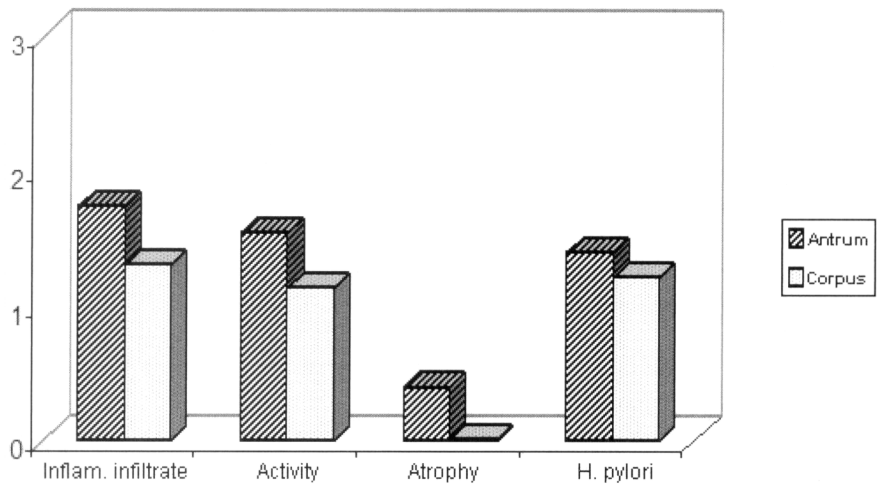

Fig. 2. *Analysis of the topographical distribution of gastritis in CIU patients compared to control dyspeptic Hp-positive control group shows a greater presence of gastric inflammation localized both in antrum and corpus gastric mucosa in CIU patients than in controls (73% vs 42.7%; p< 0.001).*

Table I. *Clinical characteristics of UBT positive and negative CIU patients.*

	UBT negative (n=65)	UBT positive (n=75)
Sex (M/F)	21/44	25/50
Age (years)	38 (17-75)	46 (17-79)*
Peptic ulcer familiarity	0	1
Gastric cancer familiarity	0	2
Past peptic ulcer	2	4
Past eradication treatment	0	4
Dyspepsia	1	3
CIU symptoms duration (months)	12 (3-168)	12 (3-264)
Angioedema	6	8
Anti-histaminic treatment	65	75

*Median (range); *p = 0.01*

DISCUSSION

Hp gastric infection has been involved in the pathogenesis of several gastric diseases, including atrophic gastritis, peptic ulcer disease and gastric lymphomas. Furthermore, the presence of the bacterium has been related to pre- and cancerous changes of gastric mucosa (12). Recent studies have suggested a possible association of Hp infection and extragastric diseases; among these, a specific association has been reported with a particular skin disease identified as chronic idiopathic urticaria (13). In the present study, the UBT revealed a prevalence of 52.4% of gastric Hp positivity in CIU patients which is, however, no different from previously reported data in similar patients (1, 14). In comparable population groups (40-50 years old), the expected prevalence of Hp positivity is around 40%, suggesting a greater prevalence of Hp in CIU patients compared to non-CIU (15). CIU Hp-positive and negative patients possessed similar clinical and personal characteristics, showing a greater mean age of Hp-positive patients compared to negative ones as the only significant difference (15). The analysis

Table II. *CIU patients with H. pylori pangastritis (n=38): different grade of gastritis severity in antrum vs corpus.*

Sydney score	Antrum	Corpus	p value
Inflam. infiltrate	1.74±0.50	1.31±0.58	p=0.0025*
Activity	1.54±0.65	1.14±0.64	p=0.0028*
Atrophy	0.40±0.73	0.02±0.16	p=0.0073*
H. Pylori	1.40±0.84	1.22±0.64	p=0.27

*Median ± SD; * t-test for paired samples*

of topographical distribution of the gastritis and its grade of severity shows a prevalent pangastritis in CIU patients compared to those dyspeptic Hp-positive, 73% *vs* 25%, respectively. Even so, the grade of severity was significantly greater in antrum than in corpus-fundus. These histological findings are supported by biochemical and symptomatological data that does not show any anaemic alteration in CIU patients with corpus-involved gastritis, in agreement with the relatively low grade of inflammation in the acid secretory mucosa and by the relatively low (4%) presence of dyspeptic symptoms (epigastric pain, bloating, early satiety, post-prandial sense of fullness) which occur in patients with only antrum-involved gastritis (16, 17). Combining the present results with data from previous studies, some hypotheses can be suggested to explain the Hp gastritis and CIU disease association (18, 19). One of the most feasible is the involvement of the gastric permeability that, increased by the Hp mucosal inflammation, allows an altered absorption of antigens and allergenic substances which, binding to specific mast-cells receptors, may determine specific symptoms related to CIU disease (18). The greater presence of pangastritis in CIU patients may have a role in increasing the mucosal area where the inflammation changes may represent the main alteration able to increase gastric permeability.

Recent studies have attempted to investigate the possible presence of alterations in gastric permeability in CIU *H. Pylori*-positive patients. In these studies, patients were subjected to an examination, the triple sugar test, performed with sucrose (a marker of gastric permeability measurement), by which an increase of gastric permeability was found which proved to be on the degree of inflammation found in the stomach (20, 21). Furthermore, the increased permeability was associated with an increased passage of allergens, food antigens and intact proteins that determine typical CIU symptoms by binding to specific receptors on mast-cells (18).

One other important mechanism in determining the CIU symptoms is related to the Hp-stimulated secretion of inflammatory mediators such as IL-1, TNF-alpha, IFN-gamma, and PAF that produce mast-cell degranulation and increased levels of histamine which is the final principal factor of CIU symptoms. From the results of these studies it can be suggested that Hp pangastritis could have a role in determining CIU symptoms in genetically predisposed subjects (22).

In conclusion, in this study it is shown that, in CIU patients, the H.p. infection determines a specific pattern of gastritis with concomitant involvement of the antrum and body-fundus. The acute and chronic inflammation occurs with a more severe level in the antrum. The efficacy is also demonstrated of *H. pylori* eradication in the symptomatology of CIU and has reinforced the theory of pseudo-allergic reaction resulting in high absorption of macromolecules (intact proteins) to increase the permeability of the mucosa at gastro-duodenal level (caused by the *H. Pylori*) in the etiopathogenesis of CIU (19, 23). The results of our study strongly suggest that HP should be specifically tested in all patients of CIU, to identify the subset of patients who are infected and who could benefit from eradication therapy. HP should be included in the diagnostic workup of all patients with CIU.

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