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INVESTIGATIVE REPORT

Role of Small Intestinal Bacterial Overgrowth and *Helicobacter pylori* Infection in Chronic Spontaneous Urticaria: A Prospective Analysis

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The aim of this study is to assess the associations between chronic spontaneous urticaria (CSU), *Helicobacter pylori* infection and small intestinal bacterial overgrowth. Forty-eight patients with CSU were studied by scoring the urticaria activity and assesing the quality of life. Patients with *H. pylori* infection ($n=11$) or small intestinal bacterial overgrowth ($n=13$) were specifically treated for one week and clinically evaluated both before and 4 weeks after the eradication therapy. Eradication of *H. pylori* infection led to a significant improvement in CSU ($p<0.002$). In contrast, eradication of small intestinal bacterial overgrowth was not associated with any clinical improvement in CSU, despite the fact that these patients had statistically significant more urticaria activity at baseline. Thus there is no evidence to support the eradication of small intestinal bacterial overgrowth in CSU, but eradication of *H. pylori* infection may result in an improvement of the disease. *Key words: chronic spontaneous urticaria; Helicobacter pylori; small intestinal bacterial overgrowth.*

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Urticaria is a heterogeneous group of diseases (1, 2). According to concensus guidelines, chronic spontaneous urticaria (CSU) (lasting more than 6 weeks) is characterized by wheals arising spontaneously without external physical stimuli (1).

Published data suggest a possible association between CSU and infections of the nasopharynx and gastrointestinal tract, focusing on *Helicobacter pylori* (HP) (1–4). However, the prevalence of HP infection in patients with CSU is uncertain, and published studies on the association between these two conditions have several methodological limitations.

Another pathological condition of the gastrointestinal tract is small intestinal bacterial overgrowth (SIBO), a condition in which excessive levels of bacteria, mainly the colonic-type species are present in the small intestine (5). An association between SIBO and rosacea has been demonstrated (6). No data have been published about the relationship between SIBO and CSU.

This aim of this study is to:

- evaluate the prevalence of SIBO and HP infection in a group of patients with CSU;
- establish whether SIBO or HP infection are associated with the severity of clinical disease;
- determine whether the eradication of SIBO or HP infection is associated with significant clinical improvement in CSU.

MATERIALS AND METHODS

Study sample

This prospective study was conducted on 51 patients hospitalized for CSU at the Dermatology Clinic, Ospedali Riuniti di Ancona, Ancona, Italy, between September 2009 and November 2010. The study was approved by the local ethics committee and conducted in conformity with the Declaration of Helsinki.

No patient was taking non-steroidal anti-inflammatory drugs, angiotensin-converting enzymes inhibitors, hormones, laxatives, ear and eye drops, or had a previous malignancy or autoimmune disease. All patients were free from any CSU-specific systemic therapy during the study.

Laboratory analyses

All patients underwent routine blood tests (complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver, thyroid and kidney function), thyroid function (T3, T4, TSH), faecal parasites, anti-streptolysin positive titre (AST), and paper radioimmunosorbent test (PRIST), for determining total serum immunoglobulin E levels (7).

An identifiable antigenic cause was ruled out since the following *in vivo* tests gave negative results:

- autologous serum skin test (ASST), which is the best *in vivo* clinical test for detection of *in vitro* basophil histamine-releasing activity, with a sensitivity of 65–71% and specificity of 78–81% (8).
- skin prick test for common food and inhalant allergens (9).

Physical urticaria was excluded in all patients.

Urea breath test and glucose breath test

All patients underwent the urea breath test (UBT) for HP infection, and the glucose breath test (GBT) for SIBO.

The UBT was performed as described by Savarino et al. (10). The reported sensitivity and specificity for the UBT are 81–100% and 80–98%, respectively (11). A positive test was defined as when the relative amount of $13CO_2$ increased > 4.0 δ $13CO_2$/ml.

The GBT was performed according to the indications of Gasbarrini et al. (12). The GBT has a sensitivity of 62.5% and a specificity of 82% (13). The test was positive for SIBO in the presence of H_2/CH_4 production > 12 ppm compared with basal values.

All patients underwent the UBT and GBT at baseline, SIBO- and HP-positive patients received specific eradication treatment for one week, and 4 weeks later (T5) they repeated the test to evaluate the efficacy of eradication treatment.

Clinical evaluation of disease activity

Severity of symptoms and their impact on patients' quality of life (QoL) were evaluated by the Urticaria Activity Score (UAS) and the Dermatology Life Quality Index (DLQI).

The UAS is a simple test to evaluate patient's skin symptoms (14, 15): all patients were asked to complete a questionnaire daily to evaluate both the number of hives (mild urticaria: < 20 wheals/24 h; moderate urticaria: 20–50 wheals/24 h; intense urticaria: > 50 wheals in 24 h or large confluent areas of wheals), and the intensity of itching (mild: present but not annoying, moderate: troublesome without interfering with normal activity or sleep; intense: severe pruritus interfering with normal daily activity or sleep). The daily severity score ranges from 0 to 6, thus the final weekly UAS score ranges from 0 to 42 (1). This test allows the evaluation of CSU symptoms in a week.

The DLQI is a simple questionnaire consisting of 10 questions, used to evaluate the impact of skin diseases on QoL. The final score ranges from 0 to 30: the higher the score, the worse the QoL (16–18). The test was completed by patients both at baseline and 4 weeks after the eradication therapy.

Administered treatments for HP infection and SIBO

Patients with HP infection were treated with a combined antibiotic therapy, according to the American College of Gastroenterology Guidelines (19). Patient with SIBO were treated with rifamixin 1,200 mg/day for one week, as suggested by Bures et al. (20).

Statistical analyses

Quantitative variables were not normally distributed, therefore non-parametric tests were used.

The patients were analysed according to the presence of HP or SIBO infections and divided into 3 groups: patients negative for both HP and SIBO, patients positive for HP, and patients positive for SIBO. Categorical variables were expressed as absolute and percentage frequencies. Comparisons between groups were analysed with the Fisher's exact test.

DLQI and UAS scores were measured at baseline and 4 weeks after the eradication treatment. The percentage variation for each score was calculated as follows: (values after–values before)/values before. DLQI and UAS at baseline and after eradication and their percentage variations were represented graphically using boxplots. Comparisons between groups were evaluated with the Kruskal-Wallis test.

The prevalences of HP and SIBO were estimated with a 95% confidence interval (95% CI) using a binomial distribution.

RESULTS

The patients were grouped according to the presence of HP or SIBO infections. Three patients were positive for both HP infection and SIBO, thus they were excluded from the study. Twenty-four patients were not infected with either HP or SIBO. Eleven patients out of 48 (22.9%; 95% CI: 12.0–37.3) were HP-infected, with a prevalence similar to the general population (20–65% of the adult population in industrialized countries) (21, 22).

The prevalence of SIBO in patients with CSU was slightly higher (27.1%; 95% CI: 15.3–41.8) than in the general asymptomatic population (0–12.5%) (23). Table I shows the main characteristics of patients evaluated at baseline: no significant differences were found between patients who were positive for HP, positive for SIBO or negative for both infections. The 3 groups were characterized by the same proportion of males, disease duration (longer than 6 months), habits (smoking), hypothyroidism, number of patients who usually took more than three drugs a day, faecal parasites, AST, PRIST levels, and age distribution. None of the patients showed hyperthyroidism.

Fig. 1 shows UAS scores evaluated at baseline, and one month after eradication, and the percentage variations between the two measurements. At baseline, patients affected by SIBO had a significantly higher UAS. After eradication patients with HP had the strongest decrease in UAS score.

Fig. 2 shows the corresponding DLQI scores. SIBO-positive patients had significantly higher scores than patients with no infection, both at baseline and after eradication. HP-positive patients had the greatest improvement in QoL: the percentage significantly decrease (median: –40)($p = 0.02$).

Table I. *Main patients' characteristics evaluated at baseline according to Helicobacter pylori (HP) infection or small intestinal bacterial overgrowth (SIBO)*

Variables	Negative *n* (%)	HP *n* (%)	SIBO *n* (%)	*p*[a]
Patients	24 (50)	11 (22.9)	13 (27.1)	
Male	11 (45.8)	2 (18.2)	4 (30.8)	0.307
Disease duration > 6 months	22 (91.7)	9 (81.8)	10 (76.9)	0.486
Smokers	7 (29.2)	4 (36.4)	8 (61.5)	0.171
Hypothyroidism	13 (54.2)	4 (36.4)	9 (69.2)	0.284
Drugs (> 3)	7 (29.2)	2 (18.2)	6 (46.2)	0.364
Faecal parasites	2 (8.3)	2 (18.2)	1 (7.7)	0.693
Prick positive	2 (8.3)	1 (9.1)	1 (7.7)	0.686
AST-positive	6 (25)	2 (18.2)	2 (15.4)	0.898
PRIST-positive	5 (20.8)	1 (9.1)	3 (23.1)	0.71
ASST-positive	2 (8.3)	0 (0)	2 (15.4)	0.548

[a]Fisher exact test.

AST: anti-streptolysin titre; PRIST: paper radioimmunosorbent test; ASST: autologous serum skin test.

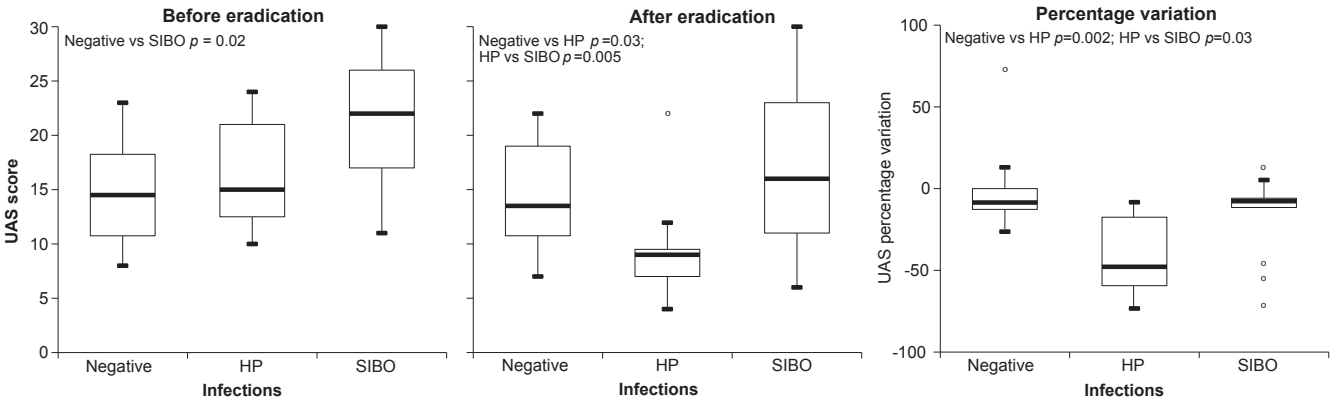

Fig. 1. Urticaria activity score (UAS) at baseline, after eradication (T5) and percentage variation between the 2 time-points (Kruskal-Wallis test).

DISCUSSION

The pathogenetic role of HP infection in CSU is still under discussion and no data have been reported about a possible clinical association between SIBO and CSU.

HP infection is common among the general population, but only some of the infected patients show CSU, and patients with CSU are not necessarily infected by HP.

Although some authors report a lack of association between HP eradication and remission of CSU (24, 25), other authors describe a beneficial role of HP eradication therapy on CSU (26–29).

Indeed, there are some reports of patients in CSU remission after every HP eradication (30). Differences in population characteristics (i.e. age, ethnic or geographical origin), criteria for diagnosis of HP infection, or breath testing methodology (substrate, instrument, gas or gases analysed and criteria to establish test positivity), may explain, at least in part, the differences among the studies (25).

The prevalence of HP infection in patients with CSU was similar to that reported for the general population of industrialized countries (21, 22) and the clinical severity of CSU in HP-infected patients was similar to that of uninfected patients.

HP infection was successfully eradicated in all treated patients, resulting in a significant improvement in patients' QoL and disease severity. These data thus agree with the results of some previous studies (26, 27). However, we have to consider that the triple therapy for HP infection shows broad-spectrum activity and could eradicate other unrecognized subclinical infections related to CSU symptoms.

Our study additionally showed that the prevalence of SIBO in patients with CSU is higher (18%) than that reported for the healthy Italian population (0–12.5% values obtained from survey of the GBT). Moreover, the presence of SIBO was correlated with more serious urticarial symptoms and a worse QoL at baseline. All SIBO-positive patients were treated successfully and none showed a persistence of bacterial overgrowth after treatment. However, the eradication of SIBO was not associated with a significant improvement in urticarial symptoms.

A limitation of this study is the lack of a control group, which was not possible because the ethics committee considered the inclusion of a control group in the protocol to be unethical. For this reason further controlled studies are required to establish the role of SIBO and HP infection in inducing or worsening CSU. However, these preliminary results indicate that there is insufficient evidence to support the use of SIBO eradication therapy in CSU. On the contrary, the eradication of HP infection could result in an improvement in the severity of CSU. Remission or improvement

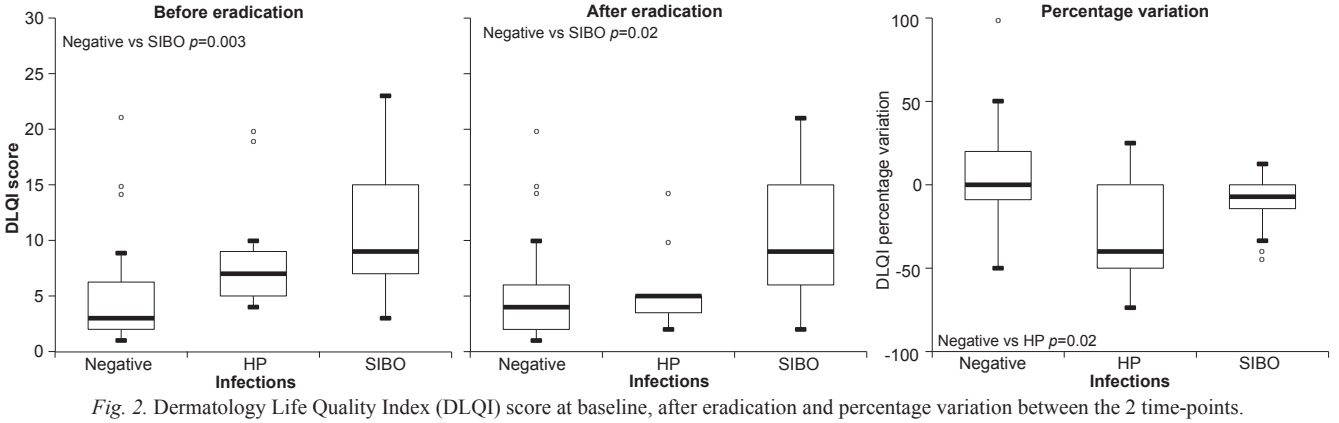

Fig. 2. Dermatology Life Quality Index (DLQI) score at baseline, after eradication and percentage variation between the 2 time-points.

in urticarial symptoms after HP eradication does not necessarily indicate a causal relationship between HP and CSU, since triple therapy could also result in the eradication of other misdiagnosed subclinical infections.

The authors declare no conflicts of interest.

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