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LETTERS TO THE EDITOR

Frequent Presence of *Helicobacter pylori* Infection in Chronic Urticaria

Sir,

In a previous pilot study we presented evidence that chronic urticaria (CU) may be associated with active infection with *Helicobacter pylori*, as it was shown that specific eradication of *H. pylori* led to clinical improvement or remission in patients with CU (1). These data are in accordance with recent findings of other groups (2–5).

We describe here a case control study to evaluate the prevalence of *H. pylori* infection in patients with CU in comparison with an age- and sex-matched control group of patients with psoriasis (PS) who have a seroprevalence of *H. pylori* infection similar to the general population (6, 7). Each patient with CU also underwent a standardized diagnostic procedure for determining other causative factors for urticaria and received cause-related therapy.

MATERIAL AND METHODS

A total of 45 inpatients with relapsing episodes of CU lasting >6 weeks (26 females, 19 males; median age 47 years; age range 18–75 years) and 45 inpatients with long-lasting severe PS (20 females, 25 males; median age 52 years; age range 22–73 years) were included in this case control study. Both groups had been hospitalized for treatment in our department. The control group comprised patients with generalized PS; none of whom had a history of urticaria. All patients gave consent to participate.

In both groups *H. pylori* infection was examined using a high validity [^{13}C]-urea breath test (8), a commercially available ELISA for specific IgG and IgA antibodies directed against *H. pylori* antigens (Bios, Gräflingen, Germany) and gastroscopy (urease test and histology).

Each CU patient was asked about the duration of the disease, episodes of concomitant angioedema, presence of physical urticaria, food and drug intolerances and dyspeptic symptoms. In addition, the presence of other focal infections, e.g. teeth, sinus, gastrointestinal tract and urogenital tract were thoroughly examined. A laboratory screening was also performed in order to determine polyclonal IgE, anti-streptolysin titres, and antinuclear antibodies. All patients received a diet consisting of tea and rusk over 3 days followed by boiled potatoes and rice over 7 days. The patients who became free of urticarial lesions under this regimen received for further diagnosis a well-defined diet with stepwise increasing content of additives, food allergens and pseudoallergens, over a period of 10 days, and the appearance of urticarial lesions was documented according to the diet protocol.

Following the diagnostic panel each patient received either a specific *H. pylori* eradication therapy with the proton pump inhibitor omeprazol combined with 2 of 3 antibiotics (erythromycin, metronidazol or amoxicillin) or a cause-related therapy with avoidance of nutritional provocation factors and of non-steroidal anti-inflammatory drugs, antibiotics against other bacterial infections or antimycotics against intestinal *Candida* infection. In idiopathic cases symptomatic therapy with antihistamines was introduced. All patients with CU were followed up over 24 weeks with repeated evaluation of disease course and *H. pylori* diagnosis. Statistical evaluation was carried out using the χ^2 test and calculating the odds ratio (Mantel-Haenzel procedure).

RESULTS

H. pylori infection diagnosed by the high validity [^{13}C]-urea breath test was found in 64% of patients with CU and in 40% of patients with PS ($p<0.05$; odds ratio (OR) 2.71; confidence interval 1.16; 6.38). Circulating specific IgG-antibodies against *H. pylori* were detected in all patients with CU and in 78% of patients with PS, and specific IgA antibodies were found in 82% of patients with CU and in all patients with PS with *H. pylori* infection. In non-infected patients with CU, antibodies against *H. pylori* of IgG type were found in 26% and of the IgA type in 33%, indicating a former *H. pylori* infection. *H. pylori* infection was significantly associated with dyspeptic symptoms in patients with CU: 86% of [^{13}C]-urea breath test-positive patients with CU had dyspeptic symptoms, in contrast to 38% of [^{13}C]-urea breath test-negative patients with CU ($p<0.05$). In 28/29 patients with CU with positive [^{13}C]-urea breath test, gastroscopy was performed to confirm *H. pylori* infection. Urease test was positive in 93% and *H. pylori* infection was confirmed by histology in 75% of patients. All patients had *H. pylori*-associated chronic active gastritis.

Unrelated to the outcome of the [^{13}C]-urea breath test our clinical attention was drawn to the presence of other concomitant focal infections. In 45% of *H. pylori*-infected and in 68% of non-infected patients with CU other focal infections were found; however, there was no statistical significance between the 2 groups. The focal infections diagnosed were gastrointestinal candidiasis (12 patients), chronic sinusitis (10 patients), urogenital infection (4 patients), bacterial/viral infections of the upper respiration tract (3 patients) and parodontitis (2 patients). In 9 patients with CU more than 1 concomitant focal infection was found.

Evidence for food intolerance was found in 48% of *H. pylori*-infected patients with CU and in 27% of non-infected patients with CU without significant difference between the 2 groups.

No significant difference between *H. pylori*-infected and non-infected patients with CU was noticed for duration of the disease, age and sex distribution, prevalence of angioedema and physical urticaria, elevation of polyclonal IgE, anti-streptolysin titres and presence of antinuclear antibodies. Episodes of angioedema were reported by 62% of the patients with urticaria, and coincidence of physical urticaria was found in 25% of the patients. Increase of polyclonal IgE was found in 48% of patients. Elevated anti-streptolysin titres were found in 12%, and slightly increased antinuclear antibodies titres were detected in 40%.

In 56% of *H. pylori*-infected patients an improvement or remission of CU was noticed after 24 weeks of successful eradication therapy. *H. pylori*-negative patients reached a comparable clearance rate if antimicrobial therapy of intestinal candidiasis or sinusitis was successful and nutritional provocation factors could be avoided. Only 40% of patients with unsuccessfully eradicated *H. pylori* showed an improvement in their CU, when simultaneously on a diets for specific foods or avoiding additives.

DISCUSSION

Based on the findings presented here we recommend that *H. pylori* diagnosis is included in the laboratory work-up of CU, preferably using the high valid [^{13}C]-urea breath test. Detection of circulating specific IgG and/or IgA antibodies against *H. pylori* does not necessarily indicate ongoing infection and titres may remain positive even after successful eradication therapy (9, 10).

From a review of the literature, there is evidence that *H. pylori* eradication therapy leads to a remission rate in CU of 29–100%, indicating a causal relationship (1–5, 11). However, a recent study reported only a 10% remission rate of CU, although *H. pylori* was successfully eradicated in most of the cases (12). In our opinion *H. pylori*-infected patients with CU should receive therapy for eradication of *H. pylori*. However, other possible causes of disease should be sought and treated. In addition, one should bear in mind that it cannot be excluded that *H. pylori* therapy leads to eradication of an occult, otherwise undiagnosed, bacterial infection.

The pathophysiological role of *H. pylori* in CU remains an enigma. Based on our current knowledge of *H. pylori* interactions with the stomach mucosa, 2 hypotheses may be discussed: firstly, *H. pylori* was shown to have a toxic effect on the mucosa cells, where the pathogen is able to induce interleukin 8 (IL-8) mRNA expression. IL-8 as well as urease and lipopolysaccharides, both secreted by *H. pylori*, may induce attraction of neutrophilic granulocytes, which are able to destroy the mucosa barrier via oxidative stress and proteolytic enzymes (13, 14). Penetration of food allergens/pseudoallergens may be promoted by this toxic cell damage. This hypothesis is supported by the fact that *H. pylori* is not an occult infection in patients with CU; it led to symptoms of chronic gastritis in all our patients. The other possibility is that *H. pylori* may be able to induce some unknown IgE-mediated or non-IgE-mediated immunomechanism, leading to urticaria disease. Experimental evidence supporting this concept demonstrated the presence of specific IgE directed against *H. pylori* on basophils and in sera (15).

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Perianal Ulcer as a Leading Symptom of Paediatric Langerhans' Cell Histiocytosis

Sir,

Langerhans' cell histiocytosis (recently termed Langerhans' cell granulomatosis) is a clonal tumour-like proliferative disease of Langerhans' cells. Positivity for HLA-DR, S-100 and CD1a, as well as the presence of Birbeck granules seen by electronmicroscopy is characteristic of these cells (1). The process affects different tissues and organs, and can be manifested either as a single lesion or as a multisystemic disease (2, 3). The course of the disease varies from an acute disseminated lethal form via benign forms with a chronic course to spontaneous healing (4, 5). Skin symptoms are important diagnostics features, which occur in 50–80% of patients with Langerhans' cell histiocytosis (6, 7). We describe here a case of paediatric Langerhans' cell histiocytosis in which perianal ulcer was a leading symptom.