ABSTRACT

Background: Chronic idiopathic urticaria (CIU) is one of the most frequent skin diseases, however its causes remain unknown in the vast majority of cases. There is increasing evidence for systemic effects of gastric Helicobacter pylori infection, which may result in extra gastrointestinal disorders. Although CIU can result from several causes, a possible relationship between chronic urticaria and Helicobacter pylori has been recently suggested.

Objective: The aim of this study is to determine the prevalence of Helicobacter pylori infection in a series of patients with CIU, and measure the effectiveness of eradication therapy on the skin disease.

Method: We assess Helicobacter pylori infection by $^{13}$C urea breath test (UBT) in 21 CIU patients. Amoxicillin, clarithromycin, and omeprazole were given to infected patients for seven days. The results of therapy were assessed by urea breath test one month after therapy. Urticaria and gastrointestinal symptoms were assessed on enrolment and for six months after eradication.

Results: Prevalence of Helicobacter pylori infection was of 71.4% (15/21). There were no differences concerning age (31.83 vs. 33.82 years) and duration of symptoms (38.40 vs. 35.38 months) in patients with respectively positive and negative UBT. Helicobacter pylori eradication rate was of 80% (12/14). Three patients had clinical improvement with total resolution of urticaria starting immediately after eradication therapy, being able to completely withdrawn antihistamine and corticosteroids therapy without complaints. In relation to the rest of the patients, these three had smaller duration of urticaria disease (14.3 vs. 43.7 months; $p = 0.038$) and greater titters in the UBT results (42.39 vs. 25.81; $p = 0.073$).

Discussion: Although some authors found convincing evidence of the involvement of Helicobacter pylori as one possible cause of chronic urticaria, our results have failed to confirm the existence of this etiological association. The most remarkable finding was that those patients who had clinical remission of disease were the ones with greater UBT titters suggesting a role for the amount of colonization by Hp in the pathogenesis of urticaria disease.

Key words: Chronic idiopathic urticaria. Helicobacter pylori. Urea breath test. Eradication therapy.

RESUMEN

Antecedentes: La urticaria crónica idiopática (UCI) es una de las enfermedades cutáneas más frecuentes, sin embargo continua siendo de causa desconocida en la mayoría de los casos. Cada vez existe una mayor evidencia de los efectos sistémicos de la infección gástrica por Helicobacter pylori (Hp), que puede producir alteraciones extragastrointestinales. Aunque la UCI puede tener una gran variedad de causas, recientemente, se ha sugerido que podría existir una relación entre urticaria crónica y Hp.
**Objetivo:** El objetivo de este estudio es determinar la prevalencia de la infección por Hp en un grupo de pacientes con UCI y comprobar la efectividad de la terapéutica de erradicación al nivel de la piel.

**Métodos:** Evaluamos la infección por Hp por medio del test de la urea en el aire espirado, marcado con C13 (TUE), en 21 pacientes. Durante 7 días, administramos amoxicilina, claritromicina y omeprazol en los pacientes con infección. Fueron evaluados, tanto la urticaria como los síntomas gastrointestinales, inicialmente y seis meses después de la erradicación.

**Resultados:** La prevalencia de la infección por Hp fue de 71,4 % (15 de 21). No se encontraron diferencias en cuanto a la edad (31,83 vs. 33,82 años) y a la duración de los síntomas (38,40 vs. 35,38 meses) en los pacientes con TUE positivo y negativo, respectivamente. La tasa de erradicación del Hp fue del 80 % (12 de 14). Tres de los pacientes presentaron mejoría clínica, que comenzó inmediatamente después de la erradicación, con resolución total de la urticaria, siendo posible la retirada de la medicación antihistamínica y corticoidea sin quejas por parte de los pacientes. En comparación con el resto de los pacientes, estos tres tuvieron una duración menor de la urticaria (14,3 vs. 43,7 meses; p = 0,038) y valores mayores en el TUE (42,39 vs. 25,81; p = 0,073).

**Discusión:** Aunque algunos autores han encontrado claramente evidencias que apuntan al Hp como posible causa de la urticaria crónica, nuestros resultados no han logrado confirmar la existencia de esta asociación etiológica. El hallazgo más importante ha sido que los pacientes con remisión clínica de la enfermedad fueron los que tuvieron valores mayores en el TUE, lo que sugiere que la cantidad de Hp que coloniza la mucosa gástrica puede tener alguna importancia en la urticaria.

**Palabras clave:** Urticaria crónica idiopática. *Helicobacter pylori*. Test de urea en aire espirado.

**INTRODUCTION**

Chronic urticaria is one of the most frequent skin diseases in allergy practice. However its causes remain unknown in the vast majority of cases. Urticaria is a common disease with prevalence ranging between 15 and 25 %\(^1\), but when chronic 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. Its cause, however, can only be found in less than 10 % of patients\(^1\).

Chronic infections and parasitic infestations have long been suggested to be an important causal factor for chronic urticaria, but this has never been consistently proven. It has been approximately 15 years since *Helicobacter pylori* (Hp) was first isolated from the human stomach\(^2\). *Helicobacter pylori*, a microaerophilic gram-negative bacteria, is associated with duodenal and gastric ulcer, gastric cancer, and atrophic gastritis and is a ubiquitous infection in the adult population\(^3\). Its prevalence is directly proportional to age and inversely correlated with socio-economic status in developing countries, in which prevalence rates reach 80 %\(^4\). The risk of infection is increased substantially by crowded living conditions and by poor sanitation.

There is increasing evidence for systemic effects of gastric Hp infection, which may be involved in extragastrointestinal disorders such as vascular, autoimmune and skin diseases. A possible relationship between chronic idiopathic urticaria (CIU) and Hp infection has been suggested in preliminary studies, in which antibiotic eradication of Hp lead to regression of urticaria in up 100 % of cases\(^5,7\).

The aim of this open prospective study is to determine the prevalence of Hp infection in a series of patients with CIU, and evaluate the effectiveness of eradication of Hp on the skin disease.

**PATIENTS AND METHODS**

We included patients attending our outpatient Immunoallergology clinic between September 1999 and February 2001, with daily, or almost daily, occurrence of urticaria for at least six weeks. Wheals should last longer than 1 hour and less than 24 hours and not cause residual pigmentation; they should not be related to local pressure areas (waistband, palm, soles) or cold stimulus. We only included previously healthy subjects, without known systemic infection or immune disease. The study was conducted in a University Hospital in the city of Oporto that assists people from urban and rural areas of the north of Portugal.

For each patient a detailed symptom history and exhaustive physical examination were performed. Gastrointestinal symptoms, urticaria exacerbation’s factors, focal infections, drug or food additives hypersensitive were assessed.

Physical urticaria like symptomatic dermographism, delayed pressure urticaria, cold urticaria, aquagenic urticaria, solar urticaria, and cholinergic urticaria were excluded. We also excluded those with a history of food allergy and those who had received antibiotics or bismuth containing drugs during the month.
prior to inclusion or that that have been treated with
proton pump inhibitors during the week prior to in-
cclusion. Patients currently participating in any clinical
trial of any kind, with concomitant diseases, condi-
tions or treatments that interfere with the evaluation
of the treatment effect, with childbearing potential
without adequate contraception or pregnancy or bre-
ast-feeding, and the ones that have been previously
enrolled in an Hp eradication study were also exclu-
ded.

All patients were informed about the study and
agreed to participate. The study was in accordance
with the Declaration of Helsinki of the World Medical
Association and was approved by the Hospital
Medical Ethics Committee.

Each patient was studied according a protocol,
that included collecting blood samples for erythrocy-
te sedimentation rate, differential blood count, com-
plete blood biochemistry, urinalysis, protein electroph-
horesis, thyroid function (free T3, free T4, Thyroid
stimulating hormone), faecal examinations for ova or
parasites, autoantibodies, circulating immunocom-
explexes, total IgE, and complement studies (C1 inhibi-
tor, C3, C4). During the study all the patients kept
their standard treatment of antihistamines and/or cor-
ticosteroids.

Determination of Helicobacter pylori infection

Hp infection was assessed by $^{13}$C urea breath test
(UBT). The breath test for Hp is a non-invasive diag-
nostic 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.
After at least 8 hours of fasting, the patient was gi-
gen 20 ml 0.1 N citric acid containing 100 mg of la-
belled Carbon $^{13}$C urea. The test is performed by the
differential detection of labelled Carbon $^{13}$C collected
in baseline breath samples and test breath samples
after ingestion.

The system utilises a Gas Isotope Ratio Mass
Spectrometer- Unicam – for the measurement of the
ratio of $^{13}$CO$_2$ to $^{12}$CO$_2$ in breath samples. Results
were expressed as change per thousand. A positive
test was defined as an average increase in the ratio
of 5/1000 over baseline.

Eradication therapy and follow-up

Amoxicillin (1g per os twice a day), clarithromycin
(500 mg per os twice a day), and omeprazole (20 mg
per os twice a day) were given to infected patients
for seven days. With this eradication therapy,
Gomollon et al had eradication rates superior to 90 %
in a Spanish population. All patients were informed
to notify the investigators about discontinuation of
the therapy and the reasons to do so. Compliance
with treatment was assessed by questionnaires.
Minimum accepted intake of total doses was 75 %.
The results of therapy were assessed by urea breath
test six weeks after therapy Hp eradication was defi-
ed as average increase of $^{13}$CO$_2$ less than 5/1000.

The clinical evaluation and follow-up were for
6 months after eradication. Recurrence of symptoms
was defined as the reappearance of urticaria symp-
toms. Cases with partial or no remission were consi-
dered as cases with persisting urticaria.

Statistical analysis

Statistical significance of data was assessed using
SPSS v 10.0 software. To study the association be-
tween CIU and the result of UBT we use the chi-squa-
re test. To study the means of numeric variables be-
tween groups with positive and negative UBT
Student’s t-test was applied.

RESULTS

Twenty females and one male patients, over
18 years with clinical and laboratory evidences of CIU
have been studied. Mean ages were 33 years (mini-
mum 19 years, maximum 55 years), with mean dura-
tion of symptoms of 36 months (7 months up to
96 months). Laboratory parameters concerning
erthrocyte sedimentation rate, differential blood
count, complete blood biochemistry, urinalysis, pro-
tein electrophoresis, thyroid function (T3, T4, TSH),
faecal examinations for ova or parasites, autoanti-
bodies, circulating immunocomplexes, and comple-
ment study didn’t show any abnormal features, as
according to our inclusion criteria. Total IgE ranged
between 19 kU/l and 1657 kU/l (median of 276 kU/L).

None of the patients reported gastrointestinal
complaints. All were on daily antihistamines and only
two were also on regular oral corticosteroids.

Fifteen patients had positive UBT, that is a preva-
ience of 71.4 %, and the mean variation of incremen-
tal increase in respiratory $^{13}$CO$_2$ was 28.81 (minimum
9.73 and maximum 58.81). One patient got pregnant
and was excluded. There were no differences in
mean duration of symptoms (38.4 vs. 35.4 months)
and mean ages (31.8 vs. 33.8 years) between groups
with negative and positive UBT respectively.

Helicobacter pylori eradication rate was of 80 %
(12/14) for one-week triple therapy with amoxacilin,
clarithromycin and omeprazol. Mean variation of increase in the second UBT was 2.75 (minimum 0.16 and maximum 2.96). In (table I) we summarize results for patients with negative and positive UBT.

Three patients (table II) had clinical improvement with total resolution of urticaria starting immediately after eradication therapy, being able to completely withdrawn antihistamine and corticosteroids therapy without complaints. In relation to the rest of the patients, these three had smaller duration of urticaria disease (14.3 vs. 43.7 months; $p = 0.038$) and greater titters in the UBT results (42.39 vs. 25.81; $p = 0.073$) (table III). There was no difference in the mean ages (35 vs. 34 years).

**DISCUSSION**

Chronic urticaria has been described to be triggered by several disease states ranging from allergic reactions to food or additives, parasitoses, microbial infections and autoimmune mechanisms. With the discovery of Hp, probably the worldwide most common chronic bacterial infection in humans, the possibility of this bacteria as a focus for chronic urticaria be-

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**Table I**

<table>
<thead>
<tr>
<th>UBT &lt; 5/1000</th>
<th>n</th>
<th>sex</th>
<th>Age (years)</th>
<th>UBT</th>
<th>Eradication efficacy*</th>
<th>UBT 2</th>
<th>Duration (months)</th>
<th>Atopy</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/6 M/5/6 F</td>
<td>6</td>
<td></td>
<td>Mean 31.8</td>
<td>1.57</td>
<td>ND</td>
<td></td>
<td>38.4</td>
<td>3/6</td>
<td>0/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minimum-Maximum 23.7-55.8</td>
<td>0.15-4.81</td>
<td></td>
<td></td>
<td>12.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Std deviation 12.2</td>
<td>1.66</td>
<td>eradicated n = 14</td>
<td></td>
<td>not eradicated n = 2</td>
<td>38.3</td>
<td></td>
</tr>
<tr>
<td>UBT &gt; 5/1000</td>
<td>15</td>
<td>15/15 F</td>
<td>Mean 33.8</td>
<td>28.81</td>
<td>2.75</td>
<td>13.24</td>
<td>35.4</td>
<td>8/15</td>
<td>3/14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minimum-Maximum 19.0-56.0</td>
<td>9.73-58.81</td>
<td>12</td>
<td>14 (80 %)</td>
<td>0.16-2.96</td>
<td>5.88-20.61</td>
<td>7-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Std deviation 8.3</td>
<td>13.94</td>
<td>0.83</td>
<td>10.41</td>
<td>30.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* One patient got pregnant and did not perform eradication therapy (n = 14); ND – not done.

**Table II**

<table>
<thead>
<tr>
<th>Sex and age (years)</th>
<th>Duration of symptoms (months)</th>
<th>Regular oral corticosteroids</th>
<th>UBT</th>
<th>UBT 2</th>
<th>Atopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, 19</td>
<td>12</td>
<td>No</td>
<td>34.99</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>Female, 56</td>
<td>7</td>
<td>Yes</td>
<td>35.73</td>
<td>1.49</td>
<td>No</td>
</tr>
<tr>
<td>Female, 29</td>
<td>24</td>
<td>Yes</td>
<td>56.46</td>
<td>0.68</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Table III**

<table>
<thead>
<tr>
<th>Clinical improvement</th>
<th>n</th>
<th>Mean Age (years)</th>
<th>Duration of symptoms (months)</th>
<th>UBT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>Mean 34.8</td>
<td>14.3</td>
<td>42.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD 19.1</td>
<td>p = 0.949</td>
<td></td>
</tr>
<tr>
<td>Without clinical improvement</td>
<td>11</td>
<td>Mean 34.0</td>
<td>43.7</td>
<td>25.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD 4.7</td>
<td>p = .038</td>
<td></td>
</tr>
</tbody>
</table>
Table IV

Studies concerning Helicobacter pylori infection and chronic idiopathic urticaria association

<table>
<thead>
<tr>
<th>Author, Year and Ref</th>
<th>Trial Type</th>
<th>Total n</th>
<th>N cases (CIU + Hp)</th>
<th>n controls</th>
<th>Prevalence (%)</th>
<th>H pylori assessment</th>
<th>Treatment (days)</th>
<th>Dyspepsia (%)</th>
<th>Improvement (%)</th>
<th>Control Group Improvement (%)</th>
<th>Association CIU-Hpylori</th>
<th>Country</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalas, 1996 (10)</td>
<td>Prospective</td>
<td>40</td>
<td>17</td>
<td>–</td>
<td>43*</td>
<td>UE Serum</td>
<td>ABM</td>
<td>NA</td>
<td>0</td>
<td>–</td>
<td>No</td>
<td>Hungary</td>
<td></td>
</tr>
<tr>
<td>Ozkaya-Bayazit, 1998 (11)</td>
<td>Prospective</td>
<td>35</td>
<td>35</td>
<td>–</td>
<td>77*</td>
<td>UE ACO (7)</td>
<td>48</td>
<td>30</td>
<td>–</td>
<td>–</td>
<td>Turkey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedi, 1998 (12)</td>
<td>Prospective</td>
<td>100</td>
<td>47</td>
<td>18</td>
<td>47*</td>
<td>Serum IgG IgA, UEB</td>
<td>ACO (7)</td>
<td>NA</td>
<td>67 Total 24 Partial</td>
<td>50</td>
<td>Yes</td>
<td>Germany</td>
<td>This study included patients with other forms of CIU, the control group were H pylori-seropositive patients with chronic urticaria without treatment</td>
</tr>
<tr>
<td>Valsecchi 1998 (13)</td>
<td>Randomised, Case-Control</td>
<td>125</td>
<td>31</td>
<td>34</td>
<td>62</td>
<td>UBT, Serum IgG, UEB</td>
<td>MCO (7)</td>
<td>NA</td>
<td>10</td>
<td>3</td>
<td>No</td>
<td>Italy</td>
<td>When the two tests were positive, gastric biopsy was performed. Patients with Helicobacter pylori infection were randomly assigned to receive triple therapy for the eradication of bacterium for one week, or no treatment</td>
</tr>
<tr>
<td>Di Campili 1998 (7)</td>
<td>Prospective</td>
<td>42</td>
<td>23</td>
<td>–</td>
<td>55</td>
<td>UBT AGL NA (7)</td>
<td>88</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>Italy</td>
<td></td>
<td>Is a descriptive study of CIU causes</td>
</tr>
<tr>
<td>Liutu 1998 (14)</td>
<td>Prospective</td>
<td>107</td>
<td>–</td>
<td>–</td>
<td>37*</td>
<td>Serum IgG</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
<td>Finland</td>
<td></td>
</tr>
<tr>
<td>Wustlich 1999 (15)</td>
<td>Prospective</td>
<td>188</td>
<td>30</td>
<td>–</td>
<td>16</td>
<td>UBT AO (14)</td>
<td>NA</td>
<td>27</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>Bonamigo 1999 (6)</td>
<td>Case-Control</td>
<td>18</td>
<td>12</td>
<td>–</td>
<td>67</td>
<td>Serum IgG</td>
<td>AMO</td>
<td>NA</td>
<td>33 Total 22 Partial</td>
<td>–</td>
<td>Yes</td>
<td>Brazil</td>
<td>Control were H Pylori negatives</td>
</tr>
<tr>
<td>Schnyder 1999 (16)</td>
<td>Double-blind placebo-controlled</td>
<td>50</td>
<td>12</td>
<td>–</td>
<td>24*</td>
<td>UBT, Serum IgG AL/Placebo</td>
<td>NA</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>Switzerland</td>
<td></td>
</tr>
<tr>
<td>Dauden 2000 (17)</td>
<td>Case-Control</td>
<td>25</td>
<td>17</td>
<td>25</td>
<td>68</td>
<td>UBT ACO (7)</td>
<td>NA</td>
<td>8 Total 16 Partial</td>
<td>–</td>
<td>No</td>
<td>Spain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erel 2000 (18)</td>
<td>Prospective</td>
<td>38</td>
<td>29</td>
<td>–</td>
<td>76*</td>
<td>UE ACO (7) All</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>No</td>
<td>Turkey</td>
<td></td>
<td>Included symptom scores</td>
</tr>
</tbody>
</table>

A - Amoxaciline; C - Claritromicine; O - Omeprazol; L - Lansoprazol; B - Bismuth; M - Metronidaizol; NA - Not Assessed; UBT- Urea Breath Test; UEB - Upper Endoscopy with Biopsy; * - Similar prevalence to the general population.
come a hypothesis. The initial studies to check for this association showed high prevalence of Hp infection in patients suffering from CIU and high remission rates of urticaria after eradication therapy. However, next studies, with broader samples, different design and methods for assessing Hp infection failed to show any significant correlation between them. Neither has become proved that Hp prevalence is higher in CIU patients. Such different results can be explained not only by different assessment tools but also by differences in the antigenicity or biological activity of the bacteria in different areas, with different socio-economic and genetical patterns of the host population. In (table IV) we present the principal studies conducted so far to study a possible link between Hp and CIU.

In our findings we failed to shown a significative association between Hp infection and CIU. However, we cannot exclude that there are some unexplored factors that could affect individual susceptibility to the bacteria. In such cases, Hp infection could be involved in the pathogenesis of urticaria. Local inflammatory response to Hp infection is dependent not only on the virulence of the organism but also on host and environmental factors. The possibility that different strains of Hp are involved, that is, strains with different genetic profiles, which may elicit more or less pathogenic responses has already been suggested. Host factors like the presence in gastric mucosa of Lewis b antigen, a receptor for Hp, could be an individual susceptibility factor for infection and indirectly for development of other pathologies related to the bacteria. An interplay among these variables leads to the release of inflammatory mediators that impair host defences and alter acid secretion. However this process remains an enigma, being tempting to speculate that structural components like adhesins or products of Hp such urease, protease, phospholipase or cytotoxines can be released and be responsible for complement activation.

One of the issues, which were not addressed in previous studies, was the absolute bacteria count and its relation with urticaria development in susceptible individuals. Several reports have already showed that UBT results correlates well with the quantitative assessment of the extent of Hp colonization in the stomach. When we compare the patients with clinical improvement with the others we found higher levels of incremental increase in respiratory $^{13}$CO$_2$ in the UBT, reflecting a larger quantity of Hp colonization. These findings suggest that the amount of bacteria could be in some patients a factor related to urticaria.

Although our results and the review of literature failed to clearly demonstrate a relationship between Hp infection and CIU, our work raises the question of the importance of the degree of Helicobacter pylori colonization to induce urticaria symptoms.