GASTRIC PATHOLOGY IN CELIAC CHILDREN AND ADULTS: THE ROLE OF *HELICOBACTER PYLORI*.

LA GASTROPATIA NEL PAZIENTE CELIACO ADULTO E BAMBINO: QUALE RUOLO PER L’*HELICOBACTER PYLORI*.

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**Key words:** celiac disease, Helicobacter pylori, villous atrophy, gastritis, duodenal biopsies

**Parole chiave:** malattia celiaca, Helicobacter pylori, atrofia villare, gastriti, biopsie duodenali
Abstract

Background: Celiac disease (CD) is an immune-mediated enteropathy that occurs in genetically susceptible individuals and is caused by an abnormal immune response to gluten. A possible relationship between Helicobacter pylori (Hp) infection and CD is not fully understood.

Objectives: The aim of our study was to compare the prevalence of Hp infection and gastric findings in CD children as compared to CD adults.

Methods: In our retrospective study 61 children (38 Females; age range 1-16.8 years; median age: 7.1 years) and 60 adults (43 Females; age range 18-74 years; median age: 35.5 years) with CD were evaluated. 65 children and 74 adults were chosen as control group age and sex matched. Diagnosis of Hp infection was based on positivity to histology and rapid urea test.

Results: All celiac enrolled were positive for EMA and/or tTG antibodies. Hp infection was diagnosed in two children and ten adults (3.3% vs. 17.5%; p<0.02). Hp infection was less frequent in celiac patients compared to the control groups, in both children and adults (p=0.005 and p=0.4, respectively). The gastric involvement in celiac patients without Hp infection was more frequent both in children (66.1% vs 11.8%; p<0.0001) and in adults (22.5% vs 16%, p= 0.3) with respect to Hp-negative controls.

Discussion and Conclusion: In conclusion, in our study we confirmed that the stomach can be involved in celiac disease both in children and adults. Sometimes, Hp infection coexists with CD diagnosis, particularly in celiac adults that can present some specific clinical findings.

Introduzione: La malattia celiaca è una enteropatia immuno-mediata che colpisce soggetti geneticamente predisposti ed è causata da una anormale risposta immune al glutine. Non è stata ancora completamente compresa la possibile relazione tra Hp e malattia celiaca.

Obiettivi: Lo scopo del nostro studio è di confrontare la patologia gastrica è l’incidenza dell’infezione da Hp tra pazienti celiaci adulti e bambini.

Metodi: Il nostro studio retrospettivo ha esaminato 61 bambini (38 femmine; age range 1-16.8; età media: 7.1 anni) e 60 adulti (43 femmine; age range 18-74 years; età media: 35.5 anni) affetti da malattia celiaca. 65 bambini e 74 adulti sono stati selezionati come gruppo di controllo.

Risultati: Tutti i pazienti celiaci selezionati sono stati positive per EMA e/o anticorpi anti-tTG. L’infezione da Hp è stata diagnosticata in due bambini e dieci adulti (3.3% vs. 17.5%; p<0.02). Tale infezione è risultata essere meno frequente nei pazienti celiaci rispetto ai gruppi di controllo, nei bambini come negli adulti (p=0.005 e p=0.4, rispettivamente). L’interessamento gastrico è stato più frequentemente rilevato nei celiaci Hp negativi rispetto a quelli affetti da infezione da Hp, nei bambini (66.1% vs 11.8%; p<0.0001) come negli adulti (22.5% vs 16%, p= 0.3).

Discussione e Conclusioni: Con il nostro studio confermiamo che l’interessamento gastrico nella malattia celiaca è possibile sia nel paziente adulto che nel pediatrico. Talvolta, l’infezione da Hp coesiste con la malattia celiaca, soprattutto nei pazienti adulti che hanno manifestazioni sintomatologiche.
Background

Celiac disease (CD) is an immune-mediated enteropathy that occurs in genetically susceptible individuals and is caused by an abnormal immune response to gluten, a component of wheat, barley and rye (1). CD can manifest itself as a typical form characterized by gastrointestinal symptoms, as an atypical form (iron-deficiency anemia, dermatitis herpetiformis, recurrent aphthous stomatitis), or be asymptomatic (silent form). Recent studies revealed that CD affects more than 1% of the general population, both in Europe (2, 3) and in North America (4).

The demonstration of histological changes of the small bowel mucosa, evaluated according to Marsh classification as modified by Oberhuber et al. (5), is the gold standard for CD diagnosis. Increasing evidence supports that the intestinal damage in celiac disease is not confined to the duodenum, but covers other tracts such as the stomach (6, 7, 8, 9, 10, 11, 12).

*Helicobacter pylori* (Hp) infection is the most prevalent gastrointestinal infection world-wide and it represents the main cause of chronic gastritis, peptic ulcer disease and gastric malignancies (13, 14, 15). Hp prevalence rates vary widely between different geographical areas and ethnic groups, increasing with age and demonstrating an acquisition rate in adults of 3% to 4% per decade (16). Even if poor socioeconomic conditions and overcrowding remain the main risk factors for Hp infection, the prevalence is rapidly decreasing even in developing countries in adult and pediatric population (17). A possible relationship between Hp infection and CD is not fully understood (12, 18, 19, 20). The aim of our study was to compare the prevalence of Hp infection, endoscopic and histologic gastric findings in CD children as compared to CD adults.

Materials and Methods

In our retrospective study, 61 children (38 Females; age ranged: from 1 to 16.8 years; median age: 7.1 years) (Group 1a) and 60 adults (43 Females; age ranged: from 18 to 74 years; median age: 35.5 years) (Group 1b) with CD were evaluated. 65 children (41 Females; age ranged: from 0.9 to 15.6 years; median age: 5.5 years)(Group 2a) and 74 adults (53 Females; age ranged: from 18 to 78 years; median age: 38 years)(Group 2b), who underwent upper endoscopy for gastrointestinal complaints without CD-related histological lesions, were chosen as control group age and sex matched. Detailed demographic, clinical and laboratory data were obtained from parents of children and from adult patients with a structured questionnaire and from patients medical files. All patients had been previously submitted to serological screening for CD. Anti-endomisium antibodies IgA (EMA) was measured by an indirect immunofluorescence method using sections from the distal portion of monkey esophagus as substrate (Eurospital, Trieste, Italy). IgA antibodies to tissue transglutaminase (tTG) were evaluated with a commercial, sandwich-type, enzyme immunoassay (Eurospital, Trieste, Italy). Patients did not perform any non invasive tests for Hp before undergoing endoscopy. In Group 1a and 2a patients, fasting overnight, after narcosis, the upper endoscopy was performed with Olympus PQ-20, GIF-E or P140 endoscopes. Group 1b and 2b patients, fasting overnight, underwent upper endoscopy using GIF-H180 or GIF-Q140 gastrosopes (Olympus Italia S.r.l. Segrate, Milan, Italy). In Group 1a and 2a during endoscopy multiple biopsies were taken (three fragments from duodenal bulb, three fragments from the distal duodenum, three fragments from gastric antrum - one for histology and two for the rapid urease test - and one from corpus). In Group 1b and 2b patients two biopsies were taken from duodenal bulb, two fragments from the distal duodenum and five from gastric mucosa (two antrum, two corpus and one angulus). Each duodenal biopsy was oriented on Millipore paper, fixed in 10% formalin and embedded in paraffin. The sections, stained with hematoxylin-eosin and Giemsa, were examined with light microscopy. Duodenal biopsies were evaluated according to Marsh classification as modified by Oberhuber (5): type 0=normal mucosa; type 1=infiltra tive (with >40 intraepithelial lymphocytes/ 100 epithelial cells); type 2=crypt hyperplasia; type 3a=mild villous atrophy; type 3b=marked villous flattening; and type 3c=total villous atrophy. Gastritis was classified and scored according to the Updated Sydney System(21). Diagnosis of Hp infection was based on positivity to histology and Rapid Urea Test (RUT).

Statistical analysis

A validated statistical package was used for comparisons between percentages (SPSS version 19.0, Chicago, IL). Baseline clinical and demographic data analysis was performed with the chi-square test and the type of correlation was determined by determining the Pearson correlation coefficient. Data were compared across groups, using either χ2 tests.
(for categorical variables) to test statistical significance. Nominal, a two-tailed probability (p) value were used and were considered to be statistically significant if p < 0.05.

Results

35 (57.4%) out of the 61 celiac children (Group 1a), showed a typical, 4 (6.6%) an atypical and 22 (36%) a silent clinical form (Table 1).

Table 1 - Clinical characteristics of Group 1a (N=61) and Group 1b (N=57) celiac patients.

<table>
<thead>
<tr>
<th>CD Clinical form</th>
<th>Group 1a N° (%)</th>
<th>Group 1b N° (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>35 (57.4)</td>
<td>26 (45.6)</td>
</tr>
<tr>
<td>Atypical</td>
<td>4 (6.6)</td>
<td>13 (22.8)</td>
</tr>
<tr>
<td>Silent</td>
<td>22 (36)</td>
<td>18 (31.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Duodenum</th>
<th>Stomach</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 3c</td>
<td>Type 3b</td>
</tr>
<tr>
<td>Duodenum</td>
<td>53 (87)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Stomach</td>
<td>20 (32.8)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

CD= celiac disease; CSG= chronic superficial gastritis; LG= lymphocytic gastritis; IG= interstitial gastritis.

The most frequent symptoms were abdominal pain, diarrhea, abdominal distension and poor weight gain. All patients were positive for EMA and/or tTG antibodies. At histological examination all patients showed villous atrophy (87% of them type 3c, 10% 3b and 3% 3a). Histological lesions of gastric mucosa were present in 21 patients (34.4%). In particular, CSG was found in 20 patients (32.8%), lymphocytic gastritis (LG) in only one patient (1.6%) (Table 1).

Hp infection was diagnosed in two (3.3%) Group 1a patients. The two Hp positive CD children had a typical CD form (one with abdominal pain, the other with abdominal distension, both without epigastric pain), chronic superficial gastritis (CSG) and severe duodenal lesions (3c type) (Table 2).

Table 2 - Clinical characteristics of Group 1a (N=2) and Group 1b (N=10) Hp+ patients.

<table>
<thead>
<tr>
<th>CD Clinical form</th>
<th>Group 1a N° (%)</th>
<th>Group 1b N° (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>2 (100)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Atypical</td>
<td>---</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Silent</td>
<td>---</td>
<td>3 (30)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Duodenum</th>
<th>Stomach</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 3c</td>
<td>Type 3b</td>
</tr>
<tr>
<td>Duodenum</td>
<td>2 (100)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Stomach</td>
<td>2 (100)</td>
<td>9 (90)</td>
</tr>
</tbody>
</table>

Hp+= Helicobacter pylori positive; CD= celiac disease; CSG= chronic superficial gastritis; LG= lymphocytic gastritis; IG= interstitial gastritis.
26 (45.6%) out of 57 celiac adults (Group 1b), showed a typical, 13 (22.8%) an atypical and 18 (31.6%) a silent clinical form (Table 1). The most frequent symptoms were abdominal distension, iron deficiency anemia, abdominal pain, diarrhea, epigastralgia and weight loss. All patients were positive for EMA and/or tTG antibodies. At histological examination 52 patients (91.2%) showed villous atrophy (61.4% of them type 3c, 28% 3b and 1.8% 3a), only one patient (1.8%) showed hyperplasic crypts (type 2) and 2 (3.5%) showed only an increase (>40) of intraepithelial lymphocytes (type 1) (Table 1).

Hp infection was diagnosed in ten patients of Group 1b (17.5%) (Group 1a vs. Group 1b: 3.3% vs. 17.5% p<0.02). Five (50%) out of the ten Hp-infected patients, had a typical, two (20%) an atypical and three (30%) a silent clinical form. Hp-infected patients complained more frequently abdominal pain (20% vs 10.6% in Hp negative; p=0.7), abdominal distension (30% vs 21.3% in Hp negative; p=0.8) and iron deficiency anemia (30% vs 12.8% in Hp negative; p=0.3).

Only one patient referred epigastric pain. The most severe histological lesions of CD (type 3c) were present in eight (80%) adults with Hp infection, while two showed 3b type. Among Hp-infected patients nine showed CSG, one an interstitial gastritis (IG) (Table 2). Among Group 1b patients, histological lesions of gastric mucosa were present in 22 patients (38.6%). In particular, CSG was found in 18 patients (31.6%), LG in three (5.3%) and IG in one patient (1.8%). LG was more common in adults than children. Hp infection in both groups occurred more frequently as superficial chronic gastritis.

Among the 65 control children (Group 2a) Hp infection was diagnosed in 14 (21.5%) patients. Histological lesions of gastric mucosa were present in 19 patients (29.2%). In particular CSG was found in 17 patients (26.1%), IG was found in one patient (1.5%) and acute gastritis (AG) in one patient (1.5%). Among Hp positive children 85.7% had CSG, one had IG and one normal gastric mucosa. The most frequent symptom was abdominal pain.

Among the 74 control adults (Group 2b) Hp infection was diagnosed in 18 (24.3%) patients (Group 2a vs Group 2b: 21.5% vs 24.3%; p=0.8). Histological lesions of gastric mucosa were present in 23 patients (31%). In particular CSG was found in 20 patients (27%), IG was found in two patients (2.7%) and AG in one patient (1.3%). Two patients (2.7%) had intestinal metaplasia. Among Hp positive adults 13 (72.2%) had CSG. The most frequent symptoms were abdominal distension, epigastralgia and abdominal pain. Hp infection was less frequent in celiac patients, both children and adults, compared to the control groups, in both children and adults (p=0.005 and p=0.4, respectively). The gastric involvement in celiac patients without Hp infection was more frequent both in children (66.1% vs 11.8%; p<0.0001) and in adults (22.5% vs 16%, p= 0.3) with respect to Hp-negative controls.

Hp-positive and negative patients show no differences in socioeconomic conditions. None of Hp-positive patients showed signs of gastric metaplasia or neutrophil infiltration.

**Discussion**

In this study we demonstrated that the gastric involvement was found in about one third of the whole series of celiacs on a gluten-containing diet: 38 patients (32.2%) had chronic superficial gastritis, 4 (3.3%) had lymphocytic gastritis and only one (0.8%) had interstitial gastritis. *Helicobacter pylori* infection was detected in 12 of them (10.2%). In adults, Hp infection was more frequent than in children and it was clinically characterized by abdominal pain, abdominal distension and iron deficiency anemia. The gastric involvement, regardless of Hp infection, was even higher in celiacs than in controls.

The Hp infection in our series was less frequently detected than other studies that reported a prevalence ranging from 21% to 83% (20, 22, 23, 24). Anyway, according to the literature, in our series higher prevalence of Hp infection has been reported in adult series than in children (as demonstrated also by the higher prevalence in adult controls than in children). Higher prevalence was also described in developing countries (22, 23, 24). Moreover, in our study the small number of subjects enrolled could have affected the final evaluation. Symptoms due to Hp infection, that always lead to the upper endoscopy, could explain the higher Hp prevalence in controls with respect to celiacs.

The only two celiac children with Hp infection showed a typical CD clinical form, type 3c histological lesions at the duodenum and chronic superficial gastritis. Instead, among the ten celiac adults with Hp infection the typical, atypical and silent CD clinical forms were equally distributed and the majority presented type 3c histological lesions and CSG. It is worth noting that in the adult series the most frequent symptoms were abdominal pain, abdominal distension and iron-deficiency anemia that were more frequent, even if not statistically significant, in Hp positive than Hp negative patients. All these three clinical findings that are widely consistent with the diagnosis of Hp infection had been variously
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described in some previous studies. The underlying mechanisms of iron-deficiency anemia could be the chronic erosive gastritis, the decreased iron absorption secondary to chronic gastritis and the iron utilization by Hp (25).

The frequent histological gastric involvement in our series confirms previous study showing that gluten intolerance may involve other portions of the gastrointestinal tract (6, 7, 8, 9, 10, 11, 12). The most frequent form was the chronic superficial gastritis both in children and in adults which was present in almost all CD patients with Hp infection but the CSG was found also in one third of CD patients without Hp infection, thus suggesting that the pathogenesis of gastric damage in CD may be affected by other factors, possibly including the delay of gastric emptying, which is reported in 30-60% of celiac (24).

In our series LG, that was evaluated following the Sydney System classification (>25 lymphocytes/100 cells), was even less frequent (2.5%) than reported by other studies performed in developing countries or using lower cut-off (> 8 lymphocytes/100 cells) (8). Anyway LG was more frequent in CD adults than in CD children. A possible underestimation of the lymphocytic gastritis prevalence in our patients should be taken into account considering the small number of patients enrolled and the exclusive biopsies sampling in the gastric in pediatric patients. However, Hayat et al. have found LG-typical lesions predominantly in the gastric antrum of celiac patients (10). No patients with Hp infection both in celiacs and controls showed LG, thus suggesting that the role of Hp in LG is quite marginal.

Conclusion
In conclusion, our study confirmed that the stomach can be involved in celiac disease both in children and adults. Sometimes Hp infection coexists with CD diagnosis, particularly in celiac adults that can present some specific clinical findings.

References


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