Inflammatory bowel disease in celiac patients

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RESUMEN

Introducción: se ha sugerido una potencial asociación entre la enfermedad celiaca y la enfermedad inflamatoria intestinal, que puede justificar que ambas enfermedades puedan presentarse en un mismo enfermo o en sus familiares de primer orden con mayor frecuencia de lo esperado.

Objetivo: determinar la prevalencia de la enfermedad de Crohn y la colitis ulcerosa en los enfermos celiacos y en sus familiares.

Método: estudio epidemiológico prospectivo transversal en un grupo de pacientes celiacos, sus familiares de primer grado y un grupo control de características epidemiológicas similares, constituido por familiares de pacientes que acuden al Servicio de Urgencias por un problema agudo. Para detectar la existencia de colitis ulcerosa y enfermedad de Crohn en los celiacos y sus familiares, se realizó una entrevista semiestructurada.

Resultados: se han incluido 86 celiacos y 432 familiares, que se han comparado con 809 controles (129 pacientes con una enfermedad aguda y 680 familiares de primer grado suyos). Se han detectado 3 casos de enfermedad de Crohn en el grupo de los enfermos celiacos y 4 casos de enfermedad de Crohn en sus familiares. Sólo se ha detectado 1 caso de enfermedad de Crohn en el grupo control (p < 0,01). No se ha identificado ningún caso de colitis ulcerosa en ninguno de los tres grupos de estudio.

Conclusión: los pacientes con enfermedad celiaca y sus familiares tienen mayor predisposición a presentar una enfermedad de Crohn, que la población control.


ABSTRACT

Introduction: a potential association between celiac disease and inflammatory bowel disease has been suggested, which may explain the fact that both disorders occasionally present in one patient or in his/her first-degree relatives more frequently than expected.

Objective: to establish the prevalence of Crohn’s disease and ulcerative colitis in celiac patients and their relatives.

Method: a cross-sectional, prospective epidemiological study in a group of celiac patients, their first-degree relatives, and a control group with similar epidemiological characteristics including the relatives of patients presenting at the ER for acute conditions. A semistructured interview was used to identify the presence of Crohn’s disease and ulcerative colitis in celiac patients and their relatives.

Results: in all, 86 celiac patients and 432 relatives were included, who were compared to 809 control subjects (129 patients with acute conditions and 680 first-degree relatives). Three cases of Crohn’s disease were identified among celiac patients, and 4 cases among their relatives. Only 1 case of Crohn’s disease was detected in the control group (p < 0.01). No cases of ulcerative colitis were detected in any of the study groups.

Conclusion: patients with celiac disease and their relatives have a greater predisposition to Crohn’s disease versus the control population.


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INTRODUCTION

Celiac disease is defined as an autoimmune bowel disease induced by gluten ingestion in genetically predisposed individuals, and is characterized by the presence of suggestive intestinal lesions that regress when gluten is discontinued (1,2). Histological lesions result from combined environmental (gluten) and genetic
factors related to class-II HLA genes DQ2 and DQ8 on the short arm of chromosome 6, which activate specific intestinal TH1 lymphocytes. In our setting HLA-DQ2 is expressed by 88-94% of patients, and HLA-DQ8 by the rest (4). The relationship between the expression of specific HLA-DQ2 and HLA-DQ8 heterodimer alleles and celiac disease suggests the presence of familial predisposition, and thus around 5% of first-degree (4,5) and even second-degree relatives (6) will develop the disease.

A characteristic of celiac disease is its association with antibody development. Some of them, including anti-gliadin, anti-endomisium, and anti-tissue transglutaminase antibodies, are of high diagnostic value and have profoundly changed both the epidemiology and recognition of clinical manifestations. Due to the use of serology for diagnosis, celiac disease ceased to be a rare disease in children with malnutrition, and became a common condition that presents at any age, both in children and adults or elderly subjects (7), that may have digestive or extradigestive symptoms, and that can be diagnosed even in non-symptomatic stages. In our setting the current prevalence of celiac disease oscillates between 1/118 in children and 1/389 among the adult population (8-10).

In turn, inflammatory bowel disease (IBD) is a chronic inflammation of the large bowel and/or the rest of the intestinal tract with unknown etiology, relapsing course, and local and/or systemic complications. The term IBD encompasses two conditions – ulcerative colitis and Crohn’s disease. As with celiac disease, immune, genetic, and environmental factors play a role in the etiopathogenesis of IBD (11-13). Prevalence is high in Europe, and a European multicenter study has shown an incidence of 10.4 and 5.6 cases/10^5 inhabitant/year for ulcerative colitis and Crohn’s disease, respectively (14).

Both conditions, celiac disease and IBD, share multiple analogies. Both are associated with genetic, immunoinflammatory diseases, share a similar immune response relative to a Th1 pattern (15), present with chronic intestinal inflammation, and their pathogenesis results from an interaction of immune, genetic, and environmental factors. It has been suggested that celiac disease and inflammatory bowel disease may relate to each other, and occur concomitantly in some patients, or predominate in some of their relatives. In this respect two case-control studies have been reviewed – one in Italy, the other in the United States – which show that IBD is more common in celiac patients versus the general population (16,17). Furthermore, a number of case or series reports have suggested an association between celiac disease and IBD, more commonly ulcerative colitis (UC) (18,19).

Based on the hypothesis that IBD prevalence is higher in celiac patients and their relatives, a cross-sectional, prospective study was designed to establish the prevalence of IBD – both of ulcerative colitis and Crohn’s disease – among celiac patients and their relatives, in order to compare it to a control, population-based group and their first-degree relatives.

**MATERIAL AND METHOD**

**Patients**

Three groups of subjects were included in the study: celiac patients, first-degree relatives of celiac patients, a control group. The celiac group was made up by all celiac patients previously diagnosed according to current criteria by serology and consistent jejunal biopsy (30) who visited “Unidad de Pruebas Funcionales Digestivas, Hospital Universitari Vall d’Hebron”, over one year. The group of family members was made by first-degree relatives of celiac patients. The control group was made up by patients with epidemiological characteristics similar to those of celiac patients who attended the Emergency Room for an acute health issue (headache, respiratory infection, nephritic colic, urticaria...), and a subgroup made up by their first-degree relatives.

**Procedure**

Over one year all patients cared for in our hospital with a biopsy-based diagnosis of celiac disease were asked to take part in the study to establish whether they had inflammatory bowel disease, or whether said disease was present in their first-degree relatives. Celiac patients and their relatives were interviewed using a semistructured questionnaire when in the hospital or by telephone. Controls were interviewed using a semistructured questionnaire administered while in the emergency room. Clinical and epidemiological data were collected, as well as the presence of Crohn’s disease or ulcerative colitis as per the diagnosis received, and whether they were on a treatment for IBD, and monitored by a gastroenterologist for IBD.

**Statistics**

Sociodemographic variables and clinical data were expressed using median and 25/75 percentile values. The prevalence of ulcerative colitis and Crohn’s disease was established independently for each study group. Differences between median values were estimated by using the Mann-Whitney or Kruskal-Wallis test. The presence of differences in qualitative variables was established by using Fisher’s exact test. The accepted level for statistical significance was < 0.05.
RESULTS

Study participants

A total of 1,357 subjects (116 celiac patients, 432 relatives, 809 controls) were enrolled. Of all 116 patients meeting the celiac group’s inclusion criteria 30 were excluded because their interview failed to occur. The group with first-degree relatives of celiac patients included 432 family members, with 5 relatives per patient on average. The control group was made up by 809 subjects, 129 patients with an acute condition and 680 of their first-degree relatives, also with 5 relatives per control subject on average. The characteristics of subjects enrolled in the study are listed in Table I. All celiac patients were on a gluten-free diet, and were also symptom- and diarrhea-free (two stools per day) at the time of inclusion. Diet adherence was adequate in 80 patients, and the remaining 6 reported intentional or non-intentional gluten ingestion on an occasional basis. Three patients were on corticoids or other immunosuppressors because of refractory celiac disease.

Table I. Major characteristics of patients with celiac disease included in the study, expressed as absolute or median value (25 percentile-75 percentile)

<table>
<thead>
<tr>
<th>Celiac patient group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>86</td>
</tr>
<tr>
<td>Age</td>
<td>34 [29-55]</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>59/27</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>6 [2-21]</td>
</tr>
<tr>
<td>Ferropenic anemia (Y/N)</td>
<td>20/59</td>
</tr>
<tr>
<td>Therapy</td>
<td>Gluten-free diet: 86</td>
</tr>
<tr>
<td></td>
<td>Steroidal therapy: 1</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressor therapy: 2</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>Dental hypoplasia: 6</td>
</tr>
<tr>
<td></td>
<td>Type-I diabetes: 1</td>
</tr>
<tr>
<td></td>
<td>IgA deficiency: 3</td>
</tr>
<tr>
<td></td>
<td>Herpetiform dermatitis: 8</td>
</tr>
<tr>
<td></td>
<td>Thyroiditis: 7</td>
</tr>
<tr>
<td></td>
<td>Hypertansaminasemia: 2</td>
</tr>
<tr>
<td></td>
<td>Epilepsy: 1</td>
</tr>
<tr>
<td></td>
<td>Polyneuropathy: 1</td>
</tr>
<tr>
<td>Compliance with diet</td>
<td>Appropriate compliance: 80</td>
</tr>
<tr>
<td></td>
<td>Non-intentional lack of compliance: 2</td>
</tr>
<tr>
<td></td>
<td>Intentional lack of compliance: 4</td>
</tr>
</tbody>
</table>

Prevalence of inflammatory bowel disease

As shown in figure 1 three cases of Crohn’s disease were identified in the celiac group, 4 cases of Crohn’s disease in the group of celiac relatives, and 1 case of Crohn’s disease in the group with 809 control subjects (Fig. 1). The relative risk for Crohn’s disease among celiac patients is 27.3, with a 95% confidence interval of 2.8-259.5. The relative risk for Crohn’s disease among the relatives of celiac patients is 7.5, with a 95% confidence interval of 0.8-66.8. All 4 cases of Crohn’s disease identified in the relatives group correspond to siblings of the celiac patient. No case of ulcerative colitis was identified in any of the study groups. The three patients identified with Crohn’s disease correspond to an AIL1B2 phenotype (age at diagnosis younger than 40 years, terminal ileum involvement, and stenosing pattern) in Montreal’s classification for Crohn’s disease (31).

The prevalence of Crohn’s disease among celiac patients (3,488 per 100,000 population) is significantly higher than in the control group (124 per 100,000 population, p < 0.01). Similarly, the prevalence of Crohn’s disease among first-degree relatives of celiac patients (926 per 100,000 population) is also statistically significantly higher versus the control group (p < 0.05). In contrast, the prevalence of ulcerative colitis in celiac patients and their first-degree relatives did not differ from that in the control group.

DISCUSSION

Based on the hypothesis that inflammatory bowel disease is more common in celiac patients and their relatives, a study has been designed to establish de prevalence of Crohn’s disease and ulcerative colitis in celiac patients and their families, and to compare it to that in a control population-based sample. The results from this cross-sectional, observational, prospective study with 86
celiac patients, 432 relatives of celiac patients, and 809 controls have shown a prevalence of Crohn’s disease among celiac patients and their families that was significantly higher than expected. This was not the case for ulcerative colitis, which has a prevalence that is not statistically different than expected in celiac patients and their relatives.

In our study the prevalence of Crohn’s disease among controls was of 124 cases per 100,000 inhabitants, a figure close to that described for the Spanish population, 116 cases per 100,000 inhabitants (32), which renders the selected control group reliable. The prevalence of Crohn’s disease observed in our study in the groups with celiac patients and their relatives is 3,488 per 100,000 and 926 per 100,000, respectively. While no statistical comparisons may be performed with the previously reported values as described for the Spanish population, the prevalence of Crohn’s disease in patients with celiac disease and their relatives is very high, and has been estimated in at least 8 times the values published for the Spanish population.

The predisposition of celiac patients and their relatives to develop Crohn’s disease may have a major clinical impact, including the need to be always aware of a potential diagnosis with Crohn’s disease in celiac patients with no adequate control when on a gluten-free diet, or in those with pathological products in their feces. Similarly, the possibility of having Crohn’s disease should also be considered for the relatives of celiac patients when consistent gastrointestinal symptoms develop.

The mechanism for the potential association between celiac disease and Crohn’s disease cannot be inferred from the present study. Both diseases are characterized by loss of tolerance to antigens (gluten and intestinal flora, respectively) in the intestinal lumen. In both conditions a local overexpression of interleukin 15 and CD4+ T-cell activation with a cytokine-related Th1 pattern are involved in the development of bowel lesions (33). This immune response pattern is not so typical of ulcerative colitis, which is more closely related to a Th2 pattern, which perhaps may explain the absence of association between ulcerative colitis and celiac disease that our study revealed.

In conclusion, the findings of this study suggest an association between celiac disease and Crohn’s disease, with a prevalence that is higher than expected both in celiac patients and their first-degree relatives.

REFERENCES


