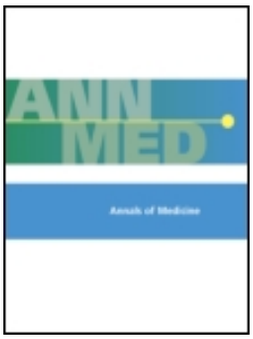

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ORIGINAL ARTICLE

Autoimmune disorders in patients affected by celiac sprue and inflammatory bowel disease

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Abstract

Background. Although clinically different, celiac sprue and inflammatory bowel disease are characterized by chronic intestinal inflammation and associated extraintestinal manifestations.

Aims. To assess and compare the presence of autoimmune disorders in patients affected by celiac sprue and inflammatory bowel disease referred to a single tertiary centre.

Methods. From October 2005 to January 2006, a total of 297 consecutive outpatients were enrolled in this cross-sectional study. Diagnoses of celiac sprue and inflammatory bowel disease were based on standard criteria. Data were recorded using an operator-assisted questionnaire: 18 autoimmune diseases, when adequately confirmed, were considered.

Results. Clinical characteristics of our patients are in conformity with those of the literature. The prevalence of associated autoimmune diseases was 25.6%, 21.1%, and 10% in patients affected by celiac sprue, Crohn's disease, and ulcerative colitis. Between the prevalence in celiac sprue and Crohn's disease there was no difference, whereas a significant difference was present between these two diseases and ulcerative colitis. The most frequent disorder in all three groups was Hashimoto's thyroiditis.

Conclusions. Celiac sprue and Crohn's disease show similar prevalence of associated autoimmune disease, higher than the prevalence in ulcerative colitis. The two diseases share the same pathogenic immunologic response and altered intestinal permeability.

Key words: *Autoimmune disease, celiac sprue, Hashimoto's thyroiditis, inflammatory bowel disease*

Introduction

Celiac sprue (CS) and the inflammatory bowel disease (IBD), Crohn's disease (CrD) and ulcerative colitis (UC), although clinically different, share some characteristics, namely chronic intestinal inflammation. The pathogenesis of these diseases is not completely understood, but genetic and environmental factors are surely involved in causing mucosal damage through an immune-mediated mechanism. Moreover, in recent years patients affected by these gastrointestinal diseases have been thought to be at increased risk of other immuno-related disorders, mainly autoimmune (AI). Furthermore, an increased prevalence of CS has been reported in patients affected by IBD, and vice versa, although this association is probably coincidental (1–5).

Many studies evaluated the co-morbidity between AI disorders and CS, which is now considered in itself an AI disease, whereas there are few and often conflicting data in CrD and UC patients in terms of both the prevalence and types of associated diseases (6–12).

This study was aimed at assessing and comparing the presence of 18 clinically expressed AI diseases in patients affected by CS and IBD.

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Key messages

- Celiac sprue and inflammatory bowel disease, namely Crohn's disease and ulcerative colitis, are characterized by chronic intestinal inflammation and associated autoimmune disorders.
- Celiac sprue and Crohn's disease show a similar prevalence 25.6% and 21.1% of associated autoimmune disorders.
- Celiac sprue and Crohn's disease share a common immunological response characterized by the presence of CD4-positive lymphocytes with a type 1 helper-T-cell phenotype.

Patients and methods

This was a cross-sectional study of consecutive adult patients with CS, CrD, or UC, who were referred to our University Hospital in Milan, Italy, between October 2005 and January 2006. The diagnosis of CS was based on positive serology (anti-endomysium and/or anti-transglutaminase antibodies), compatible histology classified as Marsh III (13), and response to the gluten-free diet (GFD). The diagnosis of IBD was based on clinical, endoscopic, radiological, and histological findings according to standardized criteria (14). Subjects with a diagnosis of undetermined colitis were excluded.

The data were collected using a two-part operator-assisted questionnaire. The first part was used to record the patients' demographic characteristics and the presence of AI diseases (diagnosis made by a specialist and/or current medications). The assessed diseases were: type 1 diabetes mellitus, autoimmune thyroiditis, primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, autoimmune haemolytic anaemia, pernicious anaemia, idiopathic thrombocytopenic purpura, alopecia areata, vitiligo, psoriasis, pemphigus, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, dermatopolymyositis, multiple sclerosis, and myasthenia gravis.

The second part of the questionnaire considered the patients' disease-specific clinical characteristics: age at diagnosis, clinical onset, course, surgery, and therapy. CrD was classified as inflammatory, stenosing, and fistulizing according to the main clinical picture at onset.

The study complied with the requirements of Italian law regarding observational studies. The nature and purpose of the survey were explained in detail to the participants, all of whom gave their written consent to data handling in accordance with the Italian law on privacy and approved by the local ethical committee.

Statistical analysis

The results are given as absolute and relative frequencies for categorical variables, and mean, standard deviation, median, minimum, and maximum values for continuous variables. The differences in the distribution of selected characteristics between the three diseases were analysed using the chi-square test, or parametric or non-parametric analysis of variance, depending on the categorical, ordinal, or continuous nature of the variable.

Univariate and multivariate logistic regression analyses were made to estimate associations between the presence of autoimmune diseases and potential determinants. The summary results for association are odds ratios (ORs) and 95% confidence intervals (95% CI).

The analyses were made using SAS software (Statistical Analysis System, SAS Institute Inc., Cary, NC, US, version 8.20); a P-value of <0.05 was considered statistically significant. All of the tests were two-sided.

Results

A total of 308 consecutive outpatients were included in the study: 117 with CS, 90 with UC, and 90 with CrD. Eleven subjects were excluded because of an incomplete or uncertain IBD diagnosis. None of our patients had concomitant CS, CrD, or UC.

Table I shows the patients' data and characteristics. The presence and type of associated AI diseases are shown in Table II. In particular, the differences in prevalence between the UC group and the CS and CrD groups were statistically significant (chi-square test, 1 df; $P=0.0044$ and $P=0.0403$, respectively), whereas the difference between CS and CrD was not (chi-square test, 1 df; $P=0.4483$). The most frequent AI disease in all three groups was Hashimoto's thyroiditis. There was no statistically significant association between the time of the diagnosis of AI and that of the intestinal disease (chi-square test, 2 df; $P=0.775$).

Regression analysis showed that among the analysed clinical and therapeutic variables only the 'type of CrD' was statistically associated with the presence of AI diseases: patients with fistulizing CrD had a lower risk of developing AI disease Relative Risk (RR 0.22; 95% CI 0.05–0.91) than those with either of the other two variants (inflammatory and fibro-stenosing).

Table I. Characteristics of patients with celiac sprue (CS), ulcerative colitis (UC), or Crohn's disease (CrD).

	CS ($n=117$)	UC ($n=90$)	CrD ($n=90$)	*P*-value
Females, *n* (%)	93 (79.5)	32 (35.6)	43 (47.8)	<0.0001[a]
Age (yrs):				
Median	34.0	48.5	48.0	<0.0001[b]
Range	18–78	18–80	20–81	
Age at diagnosis (yrs):				
Median	27.0	36	33	0.0003 [b]
Range	0–74	6–78	13–79	
Age at symptom onset (yrs):				
Median	17	34	27.5	<0.0001 [b]
Range	0–74	6–78	0–79	
Time from symptom onset to diagnosis (yrs):				
Median	2.5	0	1	<0.0001 [b]
Range	0–53	0–23	0–37	

[a] Chi-square test, 2 df.
[b] Kruskall-Wallis test, 2 df.

Specifically in the CS group, 4 cases out of 25 patients (16%) diagnosed before 14 years of age and 27 cases out of 92 patients (29.3%) diagnosed in adulthood showed associated AI diseases. Median age at enrolment was 28 years (range 18–52) for patients diagnosed before 14 years of age, and 40 years (range 20–78) for patients diagnosed in adulthood. The presence of an associated AI disease is not related to the age at clinical onset, age at diagnosis, and GFD compliance, while for each 5-year increase in current age there is a statistically significant increase in the odds of having an AI (OR 1.34, 95% CI 1.12–1.61, $P=0.0016$).

Discussion

The main result of our study, aimed to evaluate and compare the prevalence of AI disorders in patients affected by chronic intestinal diseases, was a similar frequency of AI diseases among the CS and CrD patients, which was higher than that among the UC patients. The co-morbidity of these intestinal disorders with various AI diseases has been widely reported, but the data are often conflicting because of differences in study design, the limited number of cases, and the improvement in diagnostic efficacy in the last decades. Thus it is worth underlining some aspects of our study design and population. First of all, demographic characteristics of our patients reflect those reported in the majority of published series. In fact, symptomatic CS is more frequent in females (15), and the time between symptom onset and diagnosis (16) is significantly longer than in the case of CrD or UC because of the wide variability and poor specificity of CS symptoms (17). In relation to the IBD, a slightly higher prevalence of females is usually observed among CrD patients,

Table II. Prevalence of autoimmune (AI) diseases in patients with celiac sprue (CS), ulcerative colitis (UC), or Crohn's disease (CrD).

	CS ($n=117$) *n* (%; 95% CI)	UC ($n=90$) *n* (%; 95% CI)	CrD ($n=90$) *N* (%; 95% CI)
Total AI disease	30 (25.6; 18.0–34.5)	9 (10.0; 4.7–18.1)	19 (21.1; 13.2–31.0)
Onset of AI disease before intestinal disease	19 (16.2; 10.1–24.2)	5 (5.6; 1.8–12.5)	17 (18.8; 11.4–28.5)
Types of AI disease			
Hashimoto's thyroiditis	8 (6.8; 3.0–13.0)	2 (2.2; 0.3–7.8)	4 (4.4; 1.2–11.0)
Alopecia areata	4 (3.4; 0.9–8.5)	1 (1.1; 0–6.0)	–
Psoriasis	4 (3.4; 0.9–8.5)	–	3 (3.3; 0.7–9.4)
Type 1 diabetes mellitus	3 (2.6; 0.5–7.3)	–	–
AI liver disorders	3 (2.6; 0.5–7.3)	1 (1.1; 0–6.0)	1 (1.1; 0–6.0)
Vitiligo	3 (2.6; 0.5–7.3)	1 (1.1; 0–6.0)	2 (2.2; 0.3–7.8)
Sjogren's syndrome	3 (2.6; 0.5–7.3)	1 (1.1; 0–6.0)	2 (2.2; 0.3–7.8)
Rheumatoid arthritis	2 (1.7; 0.2–6.0)	1 (1.1; 0–6.0)	3 (3.3; 0.7–9.4)
Idiopathic thrombocytopenic purpura	–	1 (1.1; 0–6.0)	2 (2.2; 0.3–7.8)
Pernicious/haemolytic anaemia	–	1 (1.1; 0–6.0)	2 (2.2; 0.3–7.8)
Others	–	–	–

95% CI = 95% binomial confidence interval.

and the contrary in UC patients (18). Our patients are all whites of Italian origin, thus race and ethnicity are not confounders in the present study. Intentionally the frequency of associated AI disorders was compared in the three groups of regularly followed-up patients and not with the general population to avoid the possible bias due to the different number of medical visits: in fact, it is possible that the patients who attend hospital more frequently and undergo a larger number of examinations have higher prevalence of associated disorders than the general population.

The highest presence of AI co-morbidity was shown in CS patients and was comparable with that reported by other Italian groups (19,20) and Finnish patients (21). Also in CrD patients the frequency of associated AI diseases is similar to that observed by Ventura et al. (19) but lower than that reported by Snook et al. (9), who also found the prevalence of associated AI disorders similar in CS and UC (6% and 7%, respectively). This discrepancy may partly be due to differences in the diagnostic approach to AI diseases over the last 15 years: in fact, the greater awareness of autoimmunity by today's physicians and the wide availability of serological markers could make the diagnosis of AI disorders more frequent. In a recent paper (22) on a large number of IBD American patients, 17% of them had a diagnosis of at least one associated immune-mediated disease. However, to confirm the difficulties in comparing the different studies on this topic, we underline that in this paper the most frequent associated disease was asthma, which shares some features with autoimmune disease but is usually not considered among the AI disorders.

In all three of our groups, the most frequent AI disease was Hashimoto's thyroiditis, whose prevalence varied from 6.8% in CS to 2.2% in UC. This finding in CS is not surprising as the association has been widely reported and the majority of gastroenterologists suggests to search for CS patients with thyroid disorders and vice versa (23,24). The prevalence of AI thyroid diseases in UC was also comparable with that published in the literature (25), whereas the prevalence found in CrD (4.4%) is more interesting, as there are only a few published cases of this association (22,26). Even if the majority of patients in the three groups developed AI disorders after the onset of intestinal symptoms, it is interesting to note that CS and CrD show similar percentages of patients suffering from AI diseases before the diagnosis of the intestinal pathology, differently from UC.

The patients affected by 'fistulizing' CrD were at lower risk of developing an associated AI disorder than those affected by the 'fibro-stenosing' type. This finding is worthy of note if we consider that some CrD patients with fistulas were treated with infliximab, which has been reported to favour the development of AI diseases (27). Our observation has never been reported before and, should it be confirmed in larger series, it might be important in terms of future clinical approaches and pathogenic interpretations.

The similarity in associated AI diseases between CS and CrD seems justifiable by their common immunological response characterized by the presence of CD4-positive lymphocytes with a type 1 helper-T-cell (Th1) phenotype, different from the Th2 phenotype predominant in UC (14). This immunological setting predisposes patients to a leaky gut condition with a disruption of the intestinal barrier in the small bowel due to the direct effect of interferon-gamma on the tight junction proteins (28). Antigens could pass from lumen to the submucosa and cause an immunological spread out of antibodies against a wide range of antigens (29).

A better understanding of this topic opens interesting possible future therapeutic perspectives. In the meantime, from a clinical point of view patients affected by celiac sprue or IBD should be carefully evaluated for AI co-morbidity in the presence of persistent symptoms or before starting immunological therapies.

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