The prevalence of celiac disease in patients with irritable bowel syndrome and its subtypes

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Abstract

Introduction: Irritable bowel syndrome (IBS) and celiac disease (CD) share some gastrointestinal symptoms. Celiac disease should be considered in a differential diagnosis of IBS.

Aim: To estimate the prevalence of predispositions to CD in patients with IBS and its subtypes.

Material and methods: The study included 48 patients (40 women, 8 men; average age: 41.1 ±14.6 years) with IBS, and a control group: 20 healthy volunteers. All participants completed a questionnaire on their current gastrointestinal symptoms and had a blood sample taken to determine the HLA-DQ2/DQ8 antigens and serum concentration of anti-tTG IgA and anti-DGP IgA and IgG.

Results: The presence of HLA-DQ2 or DQ8 was found in 50% of patients (n = 24) with IBS. In the control group the presence of HLA-DQ2 was found in 4 (20%) patients and nobody had HLA-DQ8. Increased levels of anti-tTG IgA were found in 5 (10.42%) patients with IBS, anti-DGP in 4 (8.33%), and anti-DGP IgG in 3 (6.25%). In the control group positive test result for anti-tTG was found in 2 (10%) patients; nobody had elevated anti-DGP IgA or IgG. A concomitant positive result of genetic testing and any elevated serum antibodies specific to CD was found in 12.5% of IBS patients (n = 6) and in none of the control group.

Conclusions: Patients with IBS, regardless of the subtype, significantly more often than healthy controls have the predisposing genetic factors (HLA-DQ2/DQ8) underlying the development of CD.

Introduction

Irritable bowel syndrome (IBS) is a chronic condition with variable gastrointestinal symptoms in the absence of organic abnormalities. It is characterised by chronic or recurrent abdominal pain or discomfort, bloating, and alternation of bowel habits. There are three subtypes of IBS: with predominating diarrhoea (IBS-D), constipation (IBS-C), or mixed (IBS-M). Diagnosis of IBS is based on symptom assessment: the Rome III criteria [1]. In patients over 50 years old and with alarm symptoms, colonoscopy is performed.

One of the diseases that shares some symptoms with IBS is celiac disease (CD), which is an immune-mediated small bowel enteropathy, caused by a permanent intolerance to gluten. It occurs in genetically predisposed individuals with specific histocompatibility antigens. In the course of CD, gliadin (one of the proteins belonging to the gluten) is treated with tissue transglutaminase II, which catalyses its deamidation. Deamidated gliadin peptides are more immunogenic than gliadin and bind with the human leukocyte antigen HLA-DQ2 or DQ8 receptors on antigen-presenting cells. As the next step, some gliadin epitopes are presented to Th1 lymphocytes, which in turn stimulate B cells to generate specific antibodies against tissue transglutaminase II (anti-tTG), gliadin, and deamidated gliadin peptides (anti-DGP) [2]. As a result of the inflammatory process, overgrowth of intestinal crypts and villous atrophy develops [3].

Current knowledge about the aetiopathogenesis of CD clearly shows that it occurs only in people with specific HLA histocompatibility antigens HLA-DQ2 or DQ8 [4–6]. They consist of two α and β chains forming homo- and heterozygotes. Histocompatibility antigens

HLA-DQ2 have two forms: HLA-DQ2.2 and HLA-DQ2.5. The presence of single α or β chains has also been shown [7]. Histocompatibility antigens HLA-DQ2 in the healthy population occur in 20–30% of people, and it has been shown that CD will develop in 3–4% of them in the future [8, 9].

It is estimated that 1–3% of the population suffer from CD, 10–15% of whom are not diagnosed accurately [10, 11]. It may be justified by the fact that the symptoms are often unspecific, scant, or may mimic other diseases. Celiac disease can appear at any age with varying symptomatology in children and adults.

There are four different clinical forms of CD: classical, silent, latent, and potential (genetic susceptibility for CD) [12].

The diagnosis of CD is based on clinical symptoms, histopathological criteria, and serological tests. According to current ESPGHAN guidelines [2], it is recommended that serum concentration of anti-tTG IgA and total IgA should be determined first. The use of deamidated gliadin peptide (DGP) tests has emerged in recent years. IgA antibodies against DGP have comparable sensitivity and specificity to anti-tTG. In addition, anti-DGP antibodies have higher sensitivity and specificity for IgG than anti-tTG. Thus anti-DGP may be used in screening for CD and control of gluten-free diet compliance, especially in patients with IgA deficiency [13, 14]. Anti-endomysial IgA sensitivity is less than that of anti-tTG IgA [14]. Simultaneous determination of two or more antibodies, especially the addition of anti-DGP IgA and anti-DGP IgG to anti-tTG tests, was recently suggested by Schyum and Rumessen [14]. An important element of the CD evaluation is also genetic testing. The current guidelines, both European and American, include the presence of HLA-DQ2/DQ8 as necessary for the accurate diagnosis of CD [2, 15].

Aim

Irritable bowel syndrome and CD share common manifestations. Gastrointestinal symptoms in the absence of mucosal abnormalities characterise both: IBS and latent/potential CD. Celiac disease must be considered in differential diagnosis of IBS, especially in the poorly controlled group. The aim of the present study was to estimate the prevalence of predispositions to CD in patients with IBS and its subtypes.

Material and methods

The study included 48 patients (40 women, 8 men; average age: 41.1 ±14.6 years) with a diagnosis of IBS based on Rome III criteria. The proportion of patients with IBS-D was 56.25% (n = 27), IBS-C – 29.17% (n = 14), and IBS-M – 14.58% (n = 7). The control group consisted of 20 healthy volunteers matched for age and sex (11 women, 9 men; average age: 38.2 ±14.3 years). Blood samples were taken from all patients to determine the HLA-DQ2 and DQ8 antigens by EURO-Array® at Euroimmun, Wroclaw, Poland. The presence of only a single chain α of HLA-DQ2 was not considered as a positive genetic factor for CD. In each patient serum concentration of antibodies against tissue transglutaminase II (anti-tTG IgA) and deamidated gliadin peptides (anti-DGP IgA and IgG) were measured using ELISA kits. We considered as positive level of anti-tTG three times higher than normal, according to ESPGHAN guidelines [2]. All participants in the study also completed a questionnaire on current gastrointestinal symptoms including the Rome III criteria for diagnosis of IBS.

The study protocol was approved by the Ethics Committee of the Medical University of Lodz. All the participants provided informed consent.

Results

In the study group, the presence of histocompatibility antigens HLA-DQ2 or DQ8 was found in 50% of patients (n = 24) with IBS, including 22 patients with the presence of HLA-DQ2 and 3 with HLA-DQ8 (1 IBS-D patient with both antigens). In 31.25% of the patients (n = 15) the presence of the above-mentioned antigens was not detected or only single α chains of DQ2.5 or DQ2.2 was identified – 18.75% (n = 9). As a result of analysis of histocompatibility antigens DQ2, in 7 patients the concomitant presence of both variants of the gene – DQ2.5 and DQ2.2 – was found, in 10 patients only HLA-DQ2.5, and in 5 only DQ2.2. In the control group the presence of HLA-DQ2 was detected in 4 (20%) patients, including HLA-DQ2.2 in 3 and DQ2.5 in 2, and 1 person had 2 gene variants at the same time. Single α chains of DQ2.5 or DQ2.2 were found in 8 healthy patients. HLA-DQ8 was not identified in any of the subjects.

The statistical analysis showed that patients with IBS, regardless of the subtype of the disease, significantly more often than healthy controls had the predisposing genetic factors underlying the development of CD ($p < 0.05$) (Figure 1).

The evaluation assessed the relationship between the presence of histocompatibility antigens and the subtype of IBS. Among patients with IBS-D positive HLA-DQ2/DQ8 was found in 13 (48.15%) patients, with IBS-C in 8 (57.14%), and IBS-M in 3 (42.86%) (Table I). The prevalence of genetic markers did not differ significantly among the patients from those IBS subtypes.

In all subjects the serum level of anti-tTG IgA and anti-DGP IgA and IgG was determined. Among patients with IBS, three times higher than normal levels of anti-tTG (according to ESPGHAN guidelines [2]) were

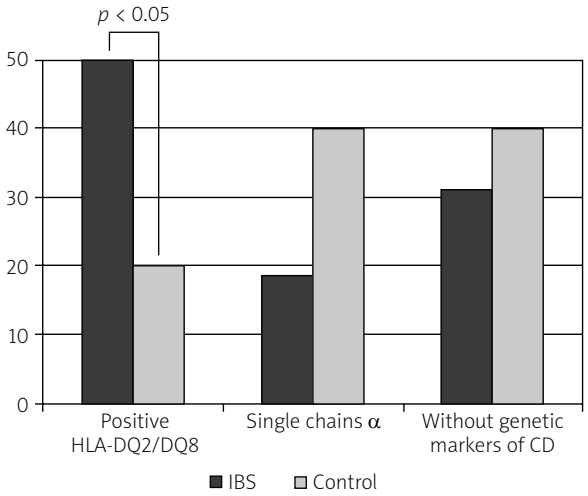

Figure 1. The prevalence of CD genetic markers in IBS patients and in the control group

CD – celiac disease, IBS – irritable bowel syndrome.

found in 5 (10.42%) patients, including 2 patients with IBS-D, and 3 with IBS-C. Elevated levels of anti-DGP IgA were detected in 4 (8.33%) patients: 1 with IBS-D, 2 with IBS-C, and 1 IBS-M. Anti-DGP IgG was found in 3 (6.25%) patients, among them 2 IBS-D and 1 IBS-C. In only 1 IBS-C patient a simultaneous significant increase in 2 overestimated antibodies was found. In the control group a positive test result for anti-tTG was found in 2 (10%) patients, and no elevated IgA or IgG anti-DGP were detected (Table II). There were no significant differences in the prevalence of anti-tTG IgA and anti-DGP IgA and IgG antibodies among IBS subtypes and the IBS and control group.

Patients with IBS and positive HLA-DQ2/DQ8 reported slightly more gastrointestinal symptoms compared with patients without these genetic markers ($p > 0.05$). Their most commonly reported symptoms were: urgency for bowel movements, feeling of incomplete evacuation, bloating, and loose stools.

In patients with IBS a concomitant positive result of genetic testing and elevated level of serum antibodies specific to CD was found in 12.5% of patients ($n = 6$), including 3 with IBS-D and 3 with IBS-C. In the control group there was no such person.

Discussion

Based on our analysis, patients with IBS significantly more often than healthy subjects had genetic markers predisposing to CD (the presence of HLA-DQ2/DQ8 in 50% of patients vs. 20% in the control group). The incidence was not significantly different among the IBS subtypes.

In a study by Wahnschaffe *et al.* 35% patients with diarrheal form of IBS had HLA-DQ2 [16]. Similar results were also obtained in our analysis, where in patients with IBS-D HLA-DQ2 the incidence amounted to 44.44%. However, in a large prospective multicentre study conducted in the USA in a group of 492 patients with non-constipation predominant IBS (NC-IBS) the incidence of haplotypes DQ2 or DQ8 (46.34%) was lower compared to the control group (52.62%) [17]. A limitation of these studies is the fact that they were carried out only in a subgroup of patients with IBS, and the results cannot be extrapolated to the entire population of those patients, including patients with IBS-C.

Researchers from the Mayo Clinic, USA demonstrated that IBS-D patients positive for HLA-DQ8, or both HLA-DQ2 and HLA-DQ8, have faster small bowel transit than those without such genetic markers. These data confirm the hypothesis that the HLA-DQ subtype is an immunogenetic predisposing factor accelerating small bowel transit after gluten exposure. It has been suggested that it causes symptoms in IBS patients who do not have CD [18]. Further studies confirmed that gluten alters bowel barrier functions in patients with IBS-D, particularly HLA-DQ2/8-positive. The mechanism of the disorder is reversible with a gluten-free diet [19].

In our study the prevalence of elevated serum levels of CD-specific antibodies among patients with IBS was found in 10.42% patients for anti-tTG IgA, 8.33% for

Table I. The incidence of histocompatibility antigens HLA-DQ2/DQ8 in patients with IBS and in the control group

Variable	HLA-DQ2.2 *n* (%)	HLA-DQ2.5 *n* (%)	Total HLA-DQ2 *n* (%)	HLA-DQ8 *n* (%)	Single chain α *n* (%)	Without HLA-DQ2/8 *n* (%)
Total IBS	12 (25)	17 (35.42)	22 (45.83)	3 (6.25)	9 (18.75)	15 (31.25)
IBS-D	7 (25.93)	9 (33.33)	12 (44.44)	2 (7.41)	5 (18.52)	9 (33.33)
IBS-C	3 (21.43)	6 (42.86)	7 (50)	1 (7.14)	1 (7.14)	5 (35.71)
IBS-M	2 (28.57)	2 (28.57)	3 (42.86)	0	3 (42.86)	1 (14.28)
Control	3 (15)	2 (10)	4 (20)	0	8 (40)	8 (40)

IBS – irritable bowel syndrome, IBS-D – diarrhoea subtype of IBS, IBS-C – constipation subtype of IBS, IBS-M – mixed subtype of IBS).

anti-DGP IgA, and 6.25% for anti-DGP IgG. These values were not statistically different compared to the control group (respectively, 10 %, 0%, and 0%). In a study carried out in the years 2007–2009 in Warsaw in a group of 150 patients with IBS diagnosed based on Rome II criteria, 32 (21.3%) patients had elevated anti-tTG antibodies and/or AGAs serum concentration; duodenal mucosa histology in all investigated patients was normal [20].

In a cross-sectional study conducted in 2008–2010 in Southeast Iran, in 5.5% of patients with IBS elevated serum anti-tTG IgA levels were found, particularly in IBS-D subtype (10.5%) [21]. In our study, the highest proportion of patients with elevated anti-tTG antibody titres was observed in the IBS-C group, but the differences were not statistically significant between the IBS subtypes.

In a study by Cash *et al.* abnormal CD antibodies were found in 7.3% of IBS patients, compared to 4.8% in healthy subjects. In the group of NC-IBS 6.51% had anti-gliadin, 1.22% anti-tTG, and 0.61% antibodies against endomysium ($p > 0.05$ vs. control for all antibodies). After gastroduodenoscopy with biopsy was performed on them, CD was diagnosed in 0.41% of patients in the NC-IBS and 0.44% in the control group ($p > 0.99$) [17]. In a study on an Asian population, 18% of a total of 186 IBS patients were positive for anti-DGP IgA, and diarrhoea was the common symptom among them. All patients with positive anti-DGP IgA observed symptom improvement after the application of a gluten-free diet [22].

A gluten-free diet in patients with IBS can bring an improvement in the gastrointestinal symptoms, particularly diarrhoea, which was confirmed in several clinical trials. In the study by Wahnschaffe *et al.* cited above, in 35% patients with IBS-D HLA-DQ2 was detected, whereas no increased anti-gliadin and anti-tTG levels were found. Nevertheless, the gluten-free diet introduced in them resulted in reduction of symptoms, diarrhoea in particular. The authors explain this as the presence of latent or potential CD in this group [16]. Further studies carried out by the same authors in a group of 145 patients with IBS-D showed that elevated serum levels of IgG antibodies against gliadin and tissue-transglutaminase were detected in 37% and the expression of HLA-DQ2 in 39% of patients. After 6 months of gluten-free diet, decreased stool frequency and relief of gastrointestinal symptoms was observed in 60% of IBS patients who were positive and in 12% who were negative for HLA-DQ2 and coeliac disease-associated serum IgG. According to Wahnschaffe *et al.*, these CD-associated serum and genetic markers can identify likely responders to a gluten-free diet in IBS-D patients [23].

Table II. The incidence of serum antibodies specific for CD in patients with IBS and in the control group

Variable	Anti-tTG IgA *n* (%)	Anti-DGP IgA *n* (%)	Anti-DGP IgG *n* (%)
Total IBS	5 (10.42)	4 (8.33)	3 (6.25)
IBS-D	2 (7.41)	1 (3.70)	2 (7.41)
IBS-C	3 (21.43)	2 (14.29)	1 (7.14)
IBS-M	0	1 (14.29)	0
Control	2 (10)	0	0

CD – celiac disease, IBS – irritable bowel syndrome, IBS-D – diarrhoea subtype of IBS, IBS-C – constipation subtype of IBS, IBS-M – mixed subtype of IBS, anti-tTG – antibodies against tissue transglutaminase II, anti-DGP – antibodies against deamidated gliadin peptides.

According to our results, a positive result of genetic testing and at the same time elevated level of serum antibodies specific to CD among patients with IBS was found in 12.5% and in none of the control group subjects. In such patients, intestinal biopsy is recommended to confirm the diagnosis of CD. Our study protocol, however, provided non- invasive testing only.

In the study by Korkut *et al.*, in 2% of patients with IBS diagnosed based on the Rome III criteria, elevated levels of anti-gliadin IgG and IgA and anti-tTG IgA were found. The diagnosis of coeliac disease was also confirmed histologically by intestinal biopsy [24]. Similar results were obtained also by El-Salhy *et al.*; based on histopathological examination of the duodenal mucosa, CD was diagnosed in 0.4% of patients with IBS, all of whom were positive for tissue transglutaminase antibodies (anti-tTG) IgA [25]. A study conducted in Jordan in a group of 742 patients with IBS confirmed CD in 24 (3.23%) patients, based on indications of anti-tTG IgA and intestinal biopsy, with significantly more common CD in IBS-D patients (IBS-D 6.8%, IBS-C 1.68%, IBS-M 2.23%) [26]. While in a study from Iran in a group of 105 IBS patients, CD was confirmed (determination of specific antibodies against endomysium or antibodies against gliadin and intestinal biopsy) in 12 (11.4%) patients [27].

In a study conducted in a group of 200 Polish patients with IBS-D, CD based on serological tests and duodenal biopsy was found in 7% of them (14 of 40 immunologically positive patients) [28].

In the case-control study of 300 subjects fulfilling the Rome II criteria for IBS, Sanders *et al.* found that the patients with IBS were seven times more likely to have biopsy-proven CD than matched controls. 4.6% of patients with IBS, who tested positive for the antibodies had active CD as compared with 0.66% of the healthy controls [29].

Several studies suggest that the incidence of CD in IBS patients is higher than in the general population: from 0.4% to 11.4% [23–25, 27, 28], especially in IBS-D subtype: 0.41–7% [17, 26, 28]. A meta-analysis by Ford et al. also showed that the prevalence of CD in IBS patients is around four times higher than in the general population [30].

However, there are also studies suggesting that the prevalence of CD in patients with IBS is not higher than that in the general population. Hin *et al.* conducted a case-finding study of CD (determination of endomysial antibodies followed by duodenal biopsy of those with positive results), and none of 132 patients with IBS had a positive result for CD [31].

In a systematic review by Cash *et al.* it was confirmed that routine serological testing for CD may be justified in patients meeting the clinical criteria for IBS [32], especially in first-degree relatives of patients with CD [33]. Another analysis conducted in 2004 also showed that the search for CD in patients with IBS can be cost effective [34].

Conclusions

Patients with IBS, regardless of the subtype of the disease, significantly more often than healthy controls have the predisposing genetic factors (HLA-DQ2/DQ8) underlying the development of CD. To identify a possible subgroup of IBS patients with latent or potential CD, genetic and serological markers of CD should be investigated. Patients with positive serology as well as HLA-DQ2/DQ8 should be carefully evaluated, including gastrointestinal biopsy, and they would probably benefit from the introduction of a gluten-free diet.

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Conflict of interest

The authors declare no conflict of interest.

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