Positive Coeliac Serology in Irritable Bowel Syndrome Patients with Normal Duodenal Biopsies: Video Capsule Endoscopy Findings and HLA-DQ Typing May Affect Clinical Management

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Abstract

Objectives. To investigate a group of IBS patients (Rome criteria) with positive coeliac serology (EMA, TTG, IgG or IgA AGA) and normal small bowel biopsies. Video capsule endoscopy (VCE) findings of the small bowell were compared with DQ-typing.

Methods. Twenty-two patients with chronic abdominal pain (with or without diarrhea) and at least one positive result of any of the coeliac serological markers (AGA, TTG, EMA) and normal duodenal biopsy were enrolled and underwent VCE. Twelve healthy volunteers with VCE served as control group. Coeliac related HLA DQ2 or DQ8 markers were determined.

Results. 12/ 22 (55%) patients had small bowel abnormalities with VCE. No mucosal abnormalities were recognized in the control group (p=0.002). Inflammatory changes were classified as moderate or pronounced. Eight patients (36%) had moderate changes and four patients (18%) demonstrated pronounced changes. Only 6 of the 21 IBS patients were positive for DQ2 and/or DQ8.

Conclusions. The patients in this study fulfilled the diagnostic Rome criteria for Irritable Bowel Syndrome. We suggest that patients with positive coeliac serology and normal duodenal biopsies should undergo HLA typing. In patients positive for DQ2 and/or DQ8, a VCE should be performed. Patients with mucosal abnormalities compatible with CD should be considered as a group distinct from IBS patients and could be tested with gluten challenge or treated with a gluten free diet.

Key words

Coeliac disease - DQ 2/8 typing – serology - irritable bowel syndrome - video capsule endoscopy - Rome criteria

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Introduction

Coeliac disease (CD) is a permanent state of intolerance to gluten i.e. alcohol insoluble protein of wheat, rye and barley which causes damage to the mucosal surface of the small intestine, in genetically predisposed individuals (1). Classical gastrointestinal (GI) symptoms of the disease in children include malabsorption and failure to thrive; while symptoms in adults may first appear following pregnancy, surgery, viral infections or severe emotional stress and present with abdominal cramping, intestinal gas, distention and bloating; chronic diarrhea or constipation (or both); anemia; and weight loss with persisting large appetite, or even subsequent weight gain. Monosymptomatic forms of CD may be more common than the multisymptomatic presentations (2); therefore knowledge about clinical symptoms is not the only reason to put this condition in the differential diagnosis.

Coeliac serological tests are commonly used to evaluate patients with GI symptoms associated with CD and patients with extra-GI or clinical conditions associated with CD, These conditions include: isolated iron deficiency; diabetes type I, Sjogren's Syndrome, Down's Syndrome, as well as autoimmune diseases in general, and first or second degree relatives of coeliacs (3). Highly sensitive and specific serological tests such as endomysial antibodies (EMA) and anti-TTG antibodies antibodies (TTG) have improved the ability to diagnose CD, as these tests demonstrated a higher specificity for CD than tests to detect antigliadin antibodies (4). Positive serology leads in general to duodenal biopsies. Nevertheless, coeliac serology might be positive, yet the ensuing duodenal biopsy may reveal normal duodenal histology. When this scenario of positive coeliac serology and normal biopsies occurs in symptomatic patients, clinicians consider such patients to suffer from Irritable Bowel Syndrome (IBS) rather than considering CD with mild histopathological abnormalities in the jejunum. Wahnschaffe et al recognized that a subgroup of IBS patients had latent/ potential CD (5). Patients with abdominal symptoms and normal duodenal biopsies were tested for CD. Positive coeliac serology obtained in duodenal fluid was recognonized in 30% of the 102 IBS study patients (5).

The HLA-DQ2 heterodimer, expressed by approximately 95% of the coeliacs, seems essential for the T-cell-response in CD. Probably the HLA-DQ8 heterodimer, expressed by 5% of the coeliacs is an alternative pathway to develop CD. Developing CD in HLA-nonDQ2nonDQ8 individuals seems rare, probably below 2%, which means that DQ2DQ8 might be of help in selecting patients for serology and/or biopsy (1). However, in general practice positive serology guides clinicians to take duodenal biopsies.

Having knowledge of the data reported by Wahnschaffe et al, we investigated a group of patients who presented with chronic unexplained abdominal pain (Rome criteria), with positive coeliac serology (AGA, TTG and/or EMA) and a normal biopsy (Marsh 0). In order to obtain detailed images of the small bowel mucosa, patients were examined by video capsule endoscopy (VCE). Capsule endoscopy has demonstrated high diagnostic yields in patients with various GI conditions and the technique provides good to excellent visualization of the mucosa of the small bowel (7). Our study objective was to examine the small bowel with VCE in a selected study population in order to evaluate and elucidate this clinical condition and to improve clinical management.

Methods

Patients were selected from the Gastroenterology Out-patient Clinic in Jerusalem who had complained about chronic abdominal pain for a duration of at least three consecutive months. A total of 20 adults (10 men, 10 women; mean age 42 yr, range 18-70) and two children (13 and 15 yr) were studied. All patients complained of recurrent abdominal pain and 14 patients reported mild diarrhea. These patients were not using NSAIDs.

Patients had a workup, which included complete blood count, TSH and liver enzymes. In patients who reported diarrhea, stools were examined for culture (Salmonella, Shigella, Campylobacter), as well as for ova and parasites. All patients underwent a gastroscopy with multiple forceps biopsies from the second and third part of the duodenum. The biopsies were oriented on paper and the pathologist was informed about coeliac serology. The duodenum was carefully examined for changes suggestive of coeliac disease. Marsh's modified classification was used for histological examination and all biopsies were described as diagnostic class "type 0" (normal), thereby not consistent with coeliac disease (1).

The indication for inclusion in this study was chronic abdominal pain (with or without diarrhea), at least one positive result of any of the coeliac serological markers (anti-endomysial antibodies IgA, anti-tTG antibodies, IgG or IgA antigliadin antibodies), and a normal duodenal biopsy (Marsh 0). Exclusion criteria included: swallowing difficulties, pregnancy, intestinal obstructive symptoms or a history of major abdominal surgery. NSAID use was not permitted. The recruitment period was from September 2002 to January 2004. Permission to grant the study was provided by the Hospital Ethics Committee and informed consent was obtained from all patients.

Following an overnight 12-hour fast, all subjects underwent VCE with the M2A video capsule (Given Imaging Ltd®, Yoqneam, Israel). All capsules were swallowed without difficulty. Subjects were allowed to resume their normal diet and routine daily activities four hours after ingestion. The cecum was reached in 21 of the 22 patients and the distal part of the ileum was seen in the remaining patient. Average gastric emptying time was 109 minutes and average small bowel transit time was 233 minutes. The transmitted video images were downloaded into a computerized system and reviewed by two gastroenterologists (both authors); conclusions were reached by consensus reading. Both readers were blinded in reference to the results of HLA typing. Data from twelve healthy volunteers (10 men, 2 women; mean age 30 yrs, range 23 - 54), who had recently participated in a motility study of the small bowel and underwent VCE served as our control group. The mean gastric emptying time was 32 minutes in controls versus 109 minutes in the study group ($p \leq 0.01$) and mean small bowel transit time 223 minutes versus 233 minutes in the study group (NS).

Grading of capsule endoscopy findings

Minimal changes: areas denuded of villi, dilated villi and erythema involving isolated areas. Patients with these findings only were classified to have mild changes and were considered normal.

Moderate changes: patients with less than five mucosal breaks and a segment of small bowel involvement of less than 10 minutes recording time.

Severe changes: patients with an ulcer of the small bowel or more than 5 mucosal breaks or a segment of small bowel involvement of more than 10 minutes recording time.

The majority of coeliacs in the Western European countries carry either the serological HLA-DQ2 or HLA-DQ8 markers, We performed a semi-automated PCR-single strand conformation polymorphism heteroduplex HLA-DQA1 and DQB1 medium resolution typing method (8).

Results

As indicated in the study criteria, all 22 patients had positive antibody test results. Nineteen patients were positive for IgG antigliadin antibodies. Five patients were positive for IgA antigliadin antibodies; four of these five were also positive for IgG antigliadin antibodies. Five of 19 were DQ2 or DQ8 positive (Table I).

Fifty-five per cent of patients were found to have small bowel abnormalities with capsule endoscopy. The most commonly affected areas were in the proximal small bowel (jejunum) and generally consisted of short segments of bowel of up to a few cm in size. Subtle changes, such as edematous folds, areas with loss of villi and dilated

Table I Characteristics of the patients included in the study

	Age	M/F	IgG AGA	IgA AGA	TTG	EMA	HLA Status	CE grading
1	22	m	18.44		na	neg		moderate
2	15	f	na		pos	pos	DQ8	
3	18	f	30	2	neg	neg		
4	73	m	11.6	2.3	na	neg		
5	29	m	25.64	6.1	neg	neg	DQ2 and DQ8	
6	31	f	20.57	15.1	neg	neg	DQ8	severe
7	47	f	11.65	2	na	neg	DQ2	moderate
8	46	f	15.99	9.74	neg	neg		
9	24	m	16		na	neg		severe
10	27	f	73	na	na	neg		moderate
11	26	m	26.4	na	neg	neg	DQ8	moderate
12	54	m	97.4		na	neg		
13	28	m	73	6	neg	neg	DQ8	moderate
14	66	f	34		na	neg		
15	43	m	18		na	neg		severe
16	52	f	na		pos	neg		severe
17	29	f	81	26	pos	neg		moderate
18	35	m	neg	14.9	neg	neg		moderate
19	54	f	30		na	neg		
20	51	m	89	9	na	neg		moderate
21	21	m	54	6	na	neg		
22	32	f	32.76	12	na	neg		

M = male, F = female, na = not available, IgG AGA = IgG antigliadin antibodies, normal < 10 u/ml, IgA AGA = IgA antigliadin antibodies, normal < 10 u/ml, TTG = Tissue transglutaminase antibodies, EMA = endomysial antibodies, CE = Capsule Endoscopy

shortened villi, were observed; moreover, more severe findings such as mucosal breaks, erosions, ulcerations and inflammatory exudates were also present (Figs.1-4).

Ten patients (45%) were classified with mild changes and considered as normal, 2/10 were DQ2/DQ8 positive, 8 patients (36%) had moderate changes, 3/8 were DQ2/DQ8 positive and four patients (18%) demonstrated pronounced changes and only one was DQ2/DQ8 positive. The patient positive for EMA and tTG had mild changes, the patient positive for tTG, positive for AGA, negative for EMA had moderate changes, whereas the patient positive for tTG, negative EMA had severe changes (Table I). In the control group of healthy volunteers, no inflammatory changes were observed (p=0.002).

Discussion

The sensitivity and specificity of coeliac serology is variable and small bowel biopsies are recommended to diagnose coeliac disease (1,8). It is known that AGA antibodies can be elevated in other medical conditions, such as congestive heart failure (9), Crohn's disease and Giardiasis (10). This simply may indicate that the integrity of the mucosal barrier in the small bowel is compromised and that antibodies to gliadin might develop, as wheat is ubiquitous in a western/middle east diet.

In this series, 21 of the 22 patients were treated as IBS patients and fulfilled the diagnostic criteria for Irritable Bowel Syndrome (Rome II classification) (6). A diagnosis of CD was ruled out in these patients, due to the fact that the small bowel biopsies were normal (1). The VCE of the small bowel did not reveal the characteristic changes of CD, such as villous atrophy, fissuring and a flat small bowel mucosa. Furthermore this patient group did not demonstrate an increased prevalence of the HLADQ2 or DQ8 genotypes, as we would expect in coeliacs. However, the presence of a positive coeliac serology test identified a large number of patients, who have unequivocal mucosal changes in the small bowel.

Patients who suffer only from chronic abdominal pain, without iron deficiency anemia or evidence of an active inflammatory process, such as arthritis or an elevated sedimentation rate, generally exhibit normal capsule endoscopy findings of the small bowel (11). The patients described in this series exhibited the clinical symptoms of IBS; nevertheless, 55% of these patients also showed both mucosal inflammatory changes in the small bowel and positive coeliac serology and therefore, should be considered as a subgroup of IBS. which maybe related to infections in the month or years before (postinfectious IBS). The problem is that coeliac disease is polygenetic (12). There is definitely a role for HLA-DQ genes, probably a major role. It might be that our patients carry some minor coeliac genes but cannot develop a proper villous atrophy due to the lack of DQ2 and/or DQ8. In future the double balloon endoscopy might be able to give us biopsies in this subgroup of IBS patients (13).

Sanders et al found a significantly increased incidence of coeliac disease among patients referred for treatment of IBS (14). The investigators suggested that all patients who fulfill Rome II diagnostic criteria for IBS with refractory symptoms or coeliac-associated disorders, should be tested for coeliac disease. We recommend that all patients with IBS symptoms be screened for CD, as the incidence of

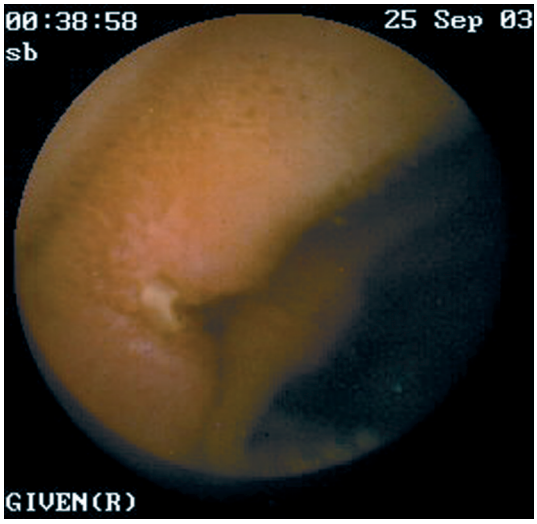

Fig.1 Capsule endoscopy image of an ulcer in the jejunum.

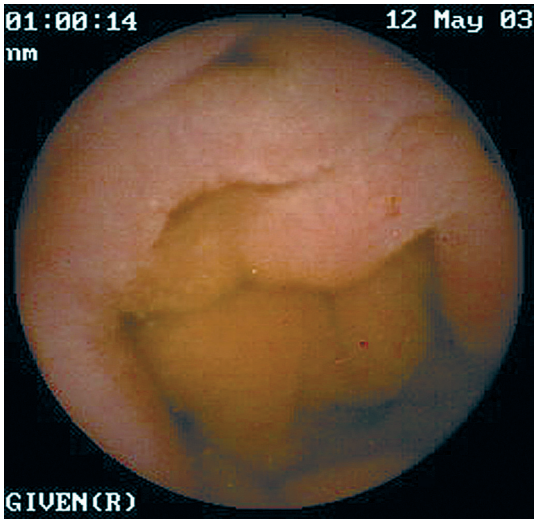

Fig.3 Edematous folds, loss of villi and inflammatory exudates covering folds.

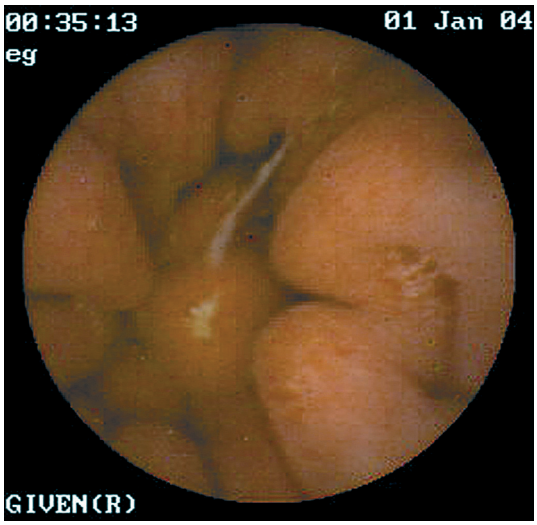

Fig.2 Edematous folds with central erosion, mucosal breaks, and inflammatory exudates.

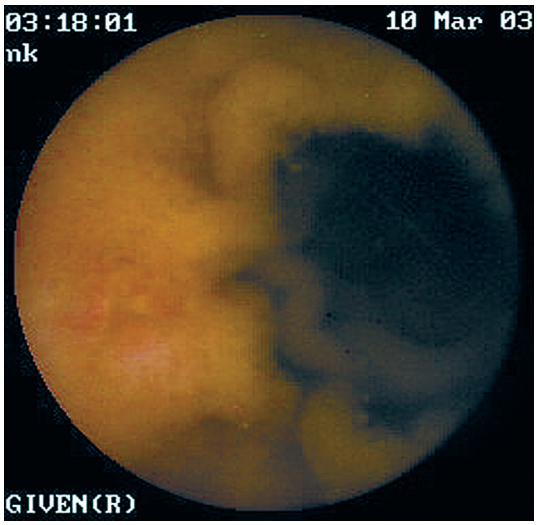

Fig.4 Ulcer with hemorrhagic margins at nine o' clock.

biopsy-proven CD in one pediatric study population was reported as high as 1:99 (14). Moreover, we would suggest patients with positive serology like tTG and EMA, and a negative duodenal biopsy merit DQ2 and DQ8 testing in combination with VCE. Considering our data, AGA is probably insufficient in discriminating for CD.

The recognition of small bowel abnormalities at capsule endoscopy in IBS patients with a CD like HLA/antibody pattern could suggest that a trial of Gluten free diet may be beneficial in this carefully selected subgroup of patients.

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