Atypical Presentation is Dominant and Typical for Coeliac Disease

Mohammad Rostami Nejad[1], Kamran Rostami[2], Mohamad Amin Pourhoseingholi[1], Ehsan Nazemalhosseini Mojarad[1], Manijeh Habibi[1], Hossein Dabiri[1], Mohammad Reza Zali [1]

1) Research Center of Gastroenterology and Liver Diseases, Shaheed Beheshti University, M.C., Tehran, Iran; 2) School of Medicine, University Hospital, Birmingham, United Kingdom

Abstract

Objectives: Atypical presentation is the most prevalent form of coeliac disease (CD) and mostly clinically indistinguishable from other gastrointestinal (GI) disorders. The first objective of this study was to determine the prevalence of CD in patients with GI symptoms and the second objective was to characterize the typical manifestations of the atypical forms of CD. **Methods**: This was a cross sectional study comprising 5,176 individuals by random sampling of self-referred people from the Tehran province, during the years 2006-2007 in a primary care setting. From 5,176 individuals, 670 with GI symptoms were selected for coeliac serology including total immunoglobulin A (IgA) and anti-tissue transglutaminase (tTG) antibodies. Those with IgA deficiency were tested with IgG tTG. **Results:** This study shows that 13% (670/5176) of self-referred patients to a general practice suffer from GI symptoms. Dyspepsia was the most common symptom in 25 seropositive cases similar to the rest of the study group. A positive anti-tTG test was found in 22 from 670 investigated subjects (17 women, 5 men) (95% CI: 1.70-4.30) and 8/670 were IgA deficient. A positive IgG tTG was detected in 3/8 IgA deficient individuals. The prevalence of CD antibodies in serologically screened samples excluding IgA-deficient was 3.3% and 3.7% when including those IgA-deficient with positive tTG-IgG. **Conclusions**: Non-specific GI symptoms seem to be the typical presentation of atypical CD. This study indicated that there is a high prevalence of CD antibodies among patients with GI symptoms (3.7%). More awareness regarding the atypical presentation of CD could be the key step in identifying asymptomatic patients.

Received: 16.01.2009 Accepted: 14.03.2009
J Gastrointestin Liver Dis
September 2009 Vol.18 No 3, 285-291
Address for correspondence: Kamran Rostami, MD, PhD.
Hon Clinical Lecturer
School of Medicine
University Hospital Birmingham, UK
Email: kamran.rostami@nhs.net

Key words

Prevalence – coeliac disease – anti-tissue transglutaminase – dyspepsia – atypical presentation – serology.

Introduction

Better awareness of "non-classical" coeliac disease (CD) and improved screening tests suggest that the prevalence of CD is underestimated in developed and developing countries [1-3]. The availability of serological tests for the diagnosis of CD during the last two decades, and a better knowledge of this disease, have permitted the identification of atypical CD [1, 4-8]. The symptoms of CD vary so widely among patients that there is no such thing as a "typical coeliac" as the individuals are affected differently. There is no correlation between the mode of presentation and the degree of mucosal damages [9]. There have been more than 200 signs and symptoms reported in association with gluten sensitivity, yet there are cases with this disorder which may have no symptoms at all [10, 11]. Terminology such as latent, silent, potential and atypical are confusing and there is a need for a better definition to cover the spectrum of gluten sensitivity.

Increasing evidence of the adverse consequences relating to delays in diagnosis and easier screening assays such as tTG [12, 13] justifies the routine screening of high risk cases [14-20]. Some preliminary reports have shown the efficacy of a case-finding strategy in both adult and pediatric populations [21-23]. This approach relies on an active role being played by primary care physicians in selecting individuals to be tested for CD. The aim of this study was to explore the etiology of GI disorders in a large cohort of symptomatic patients and to identify the typical gastrointestinal (GI) pattern of atypical CD. The atypical extra-intestinal symptoms have not been considered in this study.

Patients and Methods

Patients

This was a cross sectional study which involved 5,176

individuals randomly sampled from the population of the Tehran province, Iran during the period October 2006 – November 2007. Six hundred and seventy individuals with GI symptoms in their questionnaire were identified in a primary care setting and extensively investigated for a common GI pathology. From a total of 670 GI patients included in this study, 427 subjects were women (63.73%) and 243 subjects were men (36.27%) with a mean age of 41.61 and SD 16.55 years.

The study was approved by the Institutional Medical Ethics Committees of Research Center for Gastroenterology and Liver Disease, Shaheed Beheshti University, M.C. and all participants signed a written informed consent.

Methods

The optical density readings on enzyme-linked immunosorbent assay (ELISA) of 670 patients with GI symptoms received for tissue transglutaminase (tTG) antibody testing for CD were compared with their total IgA concentrations. Those with IgA deficiency were tested with IgG tTG.

All serological investigations were performed without knowledge of the patient status. Human antitissue transglutaminase (tTG) antibody and Immunoglobulin A were measured. Determinations of IgA tTGA antibody were carried out using a commercially available kit (AESKULISA tTG, Germany) and an enzyme-linked immunosorbent assay (ELISA) method. According to the manufacturer's instructions, when a value higher than 15.0 U/ml was recorded, the result was considered positive.

Total serum IgA values were measured by an immunoturbidometric assay (Pars Azmoon, Iran) and serum levels below 70 U/L were considered indicative of IgA deficiency. Immunoglobulin G (IgG) tTGG values were further obtained in individuals with IgA deficiency by an ELISA method, and using the commercially available kit (AESKULISA tTGG, Germany).

Statistical analysis

Descriptive statistics, the chi-square test and conditional logistic regression were carried out using SAS software in order to find significant associated factors.

Results

Around 670/5176 (13%) of cases who attended primary care for various reasons had GI symptoms (Figs. 1, 2). We found an etiology for 290/670 symptomatic cases who participated in this screening. A positive serology for coeliac disease was detected in 25/290 (Table I) and another 265/290 cases had an infectious etiology (Table II). For

Table I. Clinical and laboratory features of tTG positive patients

Subjects	Gender Male/female	Age (yrs)	tTGA	tTGA level	Total IgA	tTGG Level	Gastrointestinal symptoms
Case 1	F	64	+ve	15.22	normal	-----	Constipation, heartburn
Case 2	F	14	+ve	19.97	normal	-----	Heartburn
Case 3	M	51	+ve	26.93	normal	-----	Heartburn, abdominal pain
Case 4	F	37	+ve	25.56	normal	-----	Heartburn
Case 5	F	69	+ve	24.4	normal	-----	Abdominal pain, constipation, bloating, weight loss
Case 6	F	63	+ve	17.44	normal	-----	Heartburn, abdominal pain, bloating
Case 7	F	22	+ve	102.7	normal	-----	Heartburn
Case 8	M	81	+ve	22.59	normal	-----	Abdominal pain, weight loss
Case 9	F	42	+ve	49.68	normal	-----	Abdominal pain, constipation, bloating
Case 10	F	21	+ve	286	normal	-----	Abdominal pain, bloating
Case 11	F	14	+ve	23.23	normal	-----	Diarrhea
Case 12	M	45	+ve	20.49	normal	-----	Weight loss
Case 13	F	46	+ve	20.93	normal	-----	Abdominal pain, bloating
Case 14	F	21	+ve	16.56	normal	-----	Abdominal pain, constipation
Case 15	M	68	+ve	17.61	normal	-----	Heartburn
Case 16	F	24	+ve	83.51	normal	-----	Heartburn, bloating, weight loss
Case 17	F	44	+ve	294.6	normal	-----	Constipation, bloating, weight loss
Case 18	F	41	+ve	15.50	normal	-----	Diarrhea,
Case 19	M	64	+ve	16.73	normal	-----	Abdominal pain, constipation
Case 20	F	43	+ve	21.99	normal	-----	Heartburn, bloating
Case 21	F	33	+ve	17.79	normal	-----	Bloating
Case 22	F	29	+ve	37.80	normal	-----	Heartburn
Case 23	M	23	-ve	0.07	deficient	80.25	Constipation
Case 24	M	71	-ve	3.25	deficient	37.85	Abdominal pain
Case 25	M	20	-ve	4.22	deficient	15.07	Abdominal pain

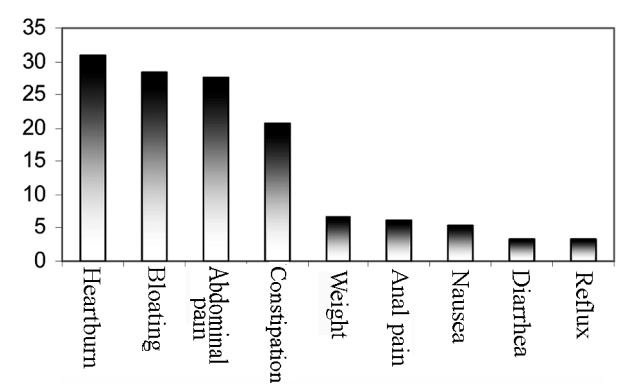

Fig 1. The frequency of gastrointestinal symptoms in 670 patients (percent)

Table II. Etiology of gastrointestinal symptoms in 290/670 GI patients

Etiology	Cases affected	Percentage
Blastocystis hominis	30/670	4.47
Giardia lamblia	41/670	6.11
Iodomoeba butchelii	13/670	1.94
Entamoeba Histolytica/ Entamoeba Dispar complex	11/670	1.64
Cryptosporidium parvum	3/670	0.44
Chilomastix mesenelli	13/670	1.94
Ascaris lumbricoides	2/670	0.3
Enterobius vermicularis	2/670	0.3
Rotavirus	150/670	22.38
tTG positive	25/670	3.7

56.7% (380/670) symptomatic cases no organic etiology was found. 293/380 (77.3%) had functional symptoms like constipation, diarrhea and dyspepsia. A number of 43/380 cases (11.3%) fulfilled the Rome III criteria for Irritable bowel syndrome. The remaining 44/380 had only self-limited short term symptoms and responded to short term symptomatic treatment (Table III).

The most prevalent symptoms in these 670 cases were dyspepsia (208/670), bloating (190/670), abdominal pain (185/670), constipation (139/670), weight loss (44/670), nausea (36/670), diarrhea (23/670) and reflux (23/670) (Fig.1). Constipation, heartburn, and bloating were significantly more prevalent in females compared to the male patients (Table IV).

Abdominal pain, heartburn, bloating and constipation were the most common symptoms found in tTG positive cases and diarrhea was found only in 2/25 cases (Table I). However, these symptoms were not specific for CD as the rest of the study group presented with similar symptoms.

A positive tTGA test was found in 22 out of 670 investigated subjects (17 women, 5 men) (95% CI: 1.70-

Table III. Functional bowel symptoms

	Conditions	Number (%)
Functional bowel symptoms	IBS	43/380 (11.3)
Non-IBS	Heartburn	147/ 380 (38.68)
	Abdominal pain	145/ 380 (38.15)
	Diarrhea	12/ 380 (3.15)
	Constipation	94/ 380 (24.73)
	Short term	44/380 (11.57)

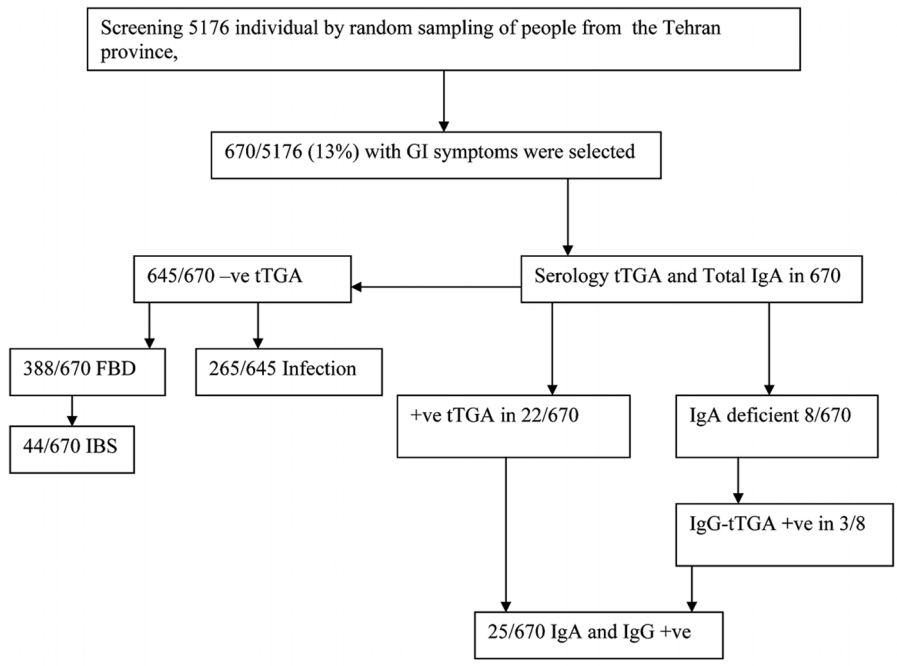

Fig 2. Flowchart or the study design. FBD functional bowel disorder, IBS irrritable bowel syndrome

Table IV. The type and frequency of symptoms in all cases, actual number and (%)

Symptoms	Females	Males	Total
Abdominal pain	142 (21.19)	43 (6.41)	185 (27.61)
Constipation	110 (16.41)	29 (4.32)	139 (20.74)
Diarrhea	13 (1.94)	10 (1.49)	23 (3.43)
Bloating	144 (21.49)	46 (6.86)	190 (28.35)
Heartburn	144 (21.49)	64(9.55)	208 (31.04)
Nausea	23 (3.43)	3 (0.44)	26 (3.88)
Weight loss	23 (3.43)	21 (3.13)	44 (6.56)
Dysphagia	18 (2.68)	6 (89)	24 (3.58)
Fecal incontinence	1 (0.14)	1 (0.14)	2 (0.29)

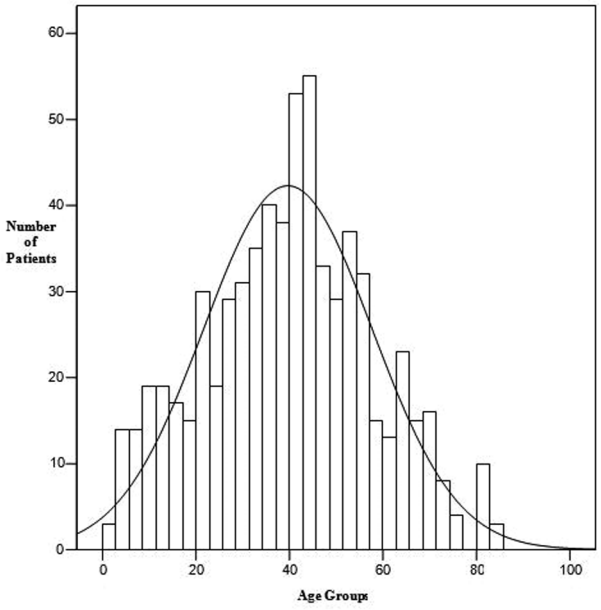

Fig 3. Histogram of age (with normal curve) for patients with gastrointestinal symptoms.

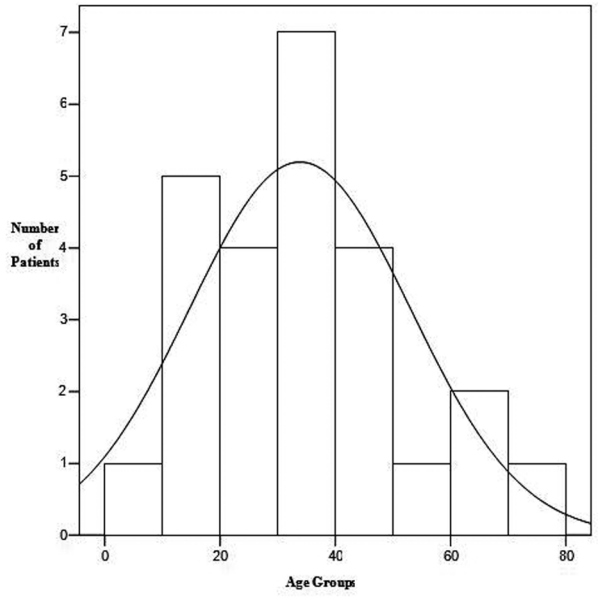

Fig 4. Histogram of age (with normal curve) for CD patients.

4.30) and 8/670 were IgA deficient. tTGG was positive in 3/8 IgA deficient. The most tTG positive patients ranged between 15- 45 years (14 patients) (Figs.3, 4)

A multivariate logistic regression was performed to assess the relationship between GI symptoms and CD. Only weight loss (OR=3.45, 95% CI: 1.15-10.30) and constipation (OR=0.33, 95% CI: 0.13-0.82) appear to be correlated significantly with CD.

Discussion

Coeliac disease is the major diagnosable food related disorder and often it is diagnosed late presenting with milder and more atypical symptoms [24]. Serologic screening studies suggest that it occurs in about 1-2.5% of the population around the world [25, 26]. However, serology does not detect a subgroup of atypical patients with milder mucosal abnormalities [27-30]. Our study included screening of patients with non-specific GI symptoms running a greater risk of CD, e.g., some of the subjects with dyspepsia and changing of bowel habits etc. Classically, the condition presented with malabsorption and failure to thrive in infancy, but this picture has now been overtaken by the much more common presentation in adults, usually with non-specific symptoms such as dyspepsia, disturbance in bowel habits or with symptoms outside the small bowel [31-39]. In this study, weight loss and constipation appeared to be correlated significantly with CD and dyspepsia was the most common symptom in the whole study group (Fig. 1). This shows that a considerable number of coeliac patients do not have demonstrable clinical or functional characteristics of the disease [7, 40]. However, this atypical presentation especially with constipation has received considerably less attention than typical forms of disease such as diarrhea and malabsorption in clinical practice (Table V).

It was suggested several decades ago that symptomatology might be related to the extent to which the small intestine is structurally involved. In other cases, symptoms arise only when the compensating hypertrophied lower small bowel is defunctioned through other factors, such as an inter-current bowel infection. However, Murray et al and others clearly identified that the symptoms are not only predominately atypical but also they do not seem to be related solely to the degree of mucosal changes [41-43]. Similarly, the sensitivity of antibodies is not influenced by clinical presentation as it does not differ between patients with typical or atypical disease [44].

Interestingly, early CD has been shown to have gluten-dependent GI symptoms even at the microscopic stage of the mucosal lesion such as Marsh 0 or Marsh I [45-47]. The main issue is not the degree of mucosal changes, but the consistency of mucosal abnormalities with gluten sensitivity [48-51]. There are gluten-sensitised lymphocytes in the mucosa and this is what gluten sensitivity means, irrespective of the degrees of mucosal damage [46, 47, 49, 52]. Unfortunately, there are no facilities to look routinely for the subtle mucosal changes even in the most modern centers. In contrast to the current guidelines restrictions,

Table V. Typical presentation of atypical CD compared to classical CD

Investigations	Classical CD	Atypical CD outside small bowel	Atypical GI like this study
	Abdominal pain Chronic diarrhea Vomiting Weight loss Foul smelling stool Fatigue Failure to thrive or short stature Delayed puberty Osteoporosis Anaemia	Obesity Dyspepsia Constipation Depression and anxiety	Abdominal pain Dyspepsia Constipation
Biochemistry and haemathology	Iron deficiency Anaemia Low serum protein levels Low serum calcium levels	Macrocytic anaemia, Vitamin B12 deficiency, Abnormal liver function tests	
Serology	Positive serology, tTGA, EMA	Negative or +ve serology, IgA deficient, or only positive in small bowel mucosa or in stool samples	
Histology	Macroscopic lesion (Marsh IIIa-IIIc)	Microscopic and macroscopic lesions Marsh 0-IIIc affecting atypical site of small bowel: bulb or terminal ileum	

we believe that symptomatic gluten sensitive cases with any degree of mucosal abnormalities would potentially benefit from a gluten free diet.

In this study, 380/670 presented functional and nonspecific bowel disorders. The symptomatology in this group was very similar to that of those with an organic etiology (Table VI). It is possible that there might be some unidentified gluten sensitive cases in this group which we have been unable to detect due to the lack of routine effective facilities [53].

Table VI. Gastrointestinal symptoms in 380 patients with functional symptoms and 290 with an organic GI disorder

Symptoms	380 with functional symptoms	290 with an organic etiology
Bloating	110 (28.9%)	80 (27.6%)
Heartburn	115 (30.30%)	93 (32.1%)
Nausea	16 (4.2%)	10 (3.4%)
Weight loss	30 (7.90%)	14 (4.8%)
Dyspepsia	18 (4.7%)	6 (2.1%)
Incontinence	1 (0.26%)	1 (0.3%)
Abdominal pain	102 (26.8%)	83 (28.6%)
Constipation	85 (22.3%)	54 (18.6%)
Diarrhea	11 (2.9%)	12 (4.1%)

Similar published analyses have shown that testing for CD in other symptomatic patients such as patients with suspected IBS is likely to be cost-effective even at a low CD prevalence (3–8%) [54-56]. Similar prevalence found in patients with dyspepsia and other atypical symptoms in this study would justify screening for gluten sensitivity in most patients with GI symptoms. Although a negative result of antibody screening does not exclude the CD diagnosis, a positive result of EMA/tTGA is associated with important histological changes. Therefore, with the limitations of serology [28, 29, 57] in detecting CD, one can assume that the prevalence of undiagnosed CD among patients with GI symptoms is even higher than the number of cases detected in this study.

One way to optimize the efficacy of screening would be by using the strategy suggested by Rashtak and Murray [5, 58]. They suggest using HLA typing as a high-sensitivity rule-out test when there is a high suspicion of CD and to use serologic testing a high-specificity rule-in test when the probability is low [5]. This strategy might be helpful in encouraging health professionals to use serology because the index of suspicion is generally low for atypical presentation. On the other hand, relying on serology alone might result in overlooking those patients with negative serology even when the suspicion is low [28-30, 57, 59]. Perhaps performing HLA typing in seronegatives would give some more degree of reassurance in ruling it out as suggested by Hadithi et al [58].

Finally, it is time to forget the classical GI presentation and focus on non-specific specificities of the CD spectrum when the health-related life quality of coeliac patients with atypical presentation is impaired. Implementing a new diagnostic strategy with a high index of suspicion based on recent evidence on atypical forms of CD would be the key step in identifying patients without symptoms.

Conflicts of interest

None to declare.

References

1. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology 2006; 131: 1981-2002.
2. Rostami K, Malekzadeh R, Shahbazkhani B, Akbari MR, Catassi C. Coeliac disease in Middle Eastern countries: a challenge for the

evolutionary history of this complex disorder? Dig Liver Dis 2004; 36: 694-697.
3. de Freitas IN, Sipahi AM, Damiao AO, et al. Celiac disease in Brazilian adults. J Clin Gastroenterol 2002; 34: 430-434.
4. Pereira MA, Ortiz-Agostinho CL, Nishitokukado I, et al. Prevalence of celiac disease in an urban area of Brazil with predominantly European ancestry. World J Gastroenterol 2006; 12: 6546-5650.
5. Rashtak S, Murray JA. Tailored testing for celiac disease. Ann Intern Med 2007; 147: 339-341.
6. Craig D, Robins G, Howdle PD. Advances in celiac disease. Curr Opin Gastroenterol 2007; 23: 142-148.
7. Shahbazkhani B, Forootan M, Merat S, et al. Coeliac disease presenting with symptoms of irritable bowel syndrome. Aliment Pharmacol Ther 2003; 18: 231-235.
8. Ludvigsson JF, Askling J, Ekbom A, Montgomery SM. Diagnosis underlying appendectomy and coeliac disease risk. Dig Liver Dis 2006; 38: 823-828.
9. Brar P, Kwon GY, Egbuna, II, et al. Lack of correlation of degree of villous atrophy with severity of clinical presentation of coeliac disease. Dig Liver Dis 2007; 39: 26-29.
10. Ozaslan E, Akkorlu S, Eskioglu E, Kayhan B. Prevalence of silent celiac disease in patients with dyspepsia. Dig Dis Sci 2007; 52: 692-697.
11. Waldo RT. Iron-deficiency anemia due to silent celiac sprue. Proc (Bayl Univ Med Cent) 2002; 15: 16-17.
12. Shamir R, Eliakim R, Lahat N, Sobel E, Lerner A. ELISA of anti-endomysial antibodies in the diagnosis of celiac disease: comparison with immunofluorescence assay of anti-endomysial antibodies and tissue transglutaminase antibodies. Isr Med Assoc J 2002; 4: 594-596.
13. Catassi C. Where is celiac disease coming from and why? J Pediatr Gastroenterol Nutr 2005; 40: 279-282.
14. Collin P, Hallstrom O, Maki M, Viander M, Keyrilainen O. Atypical coeliac disease found with serologic screening. Scand J Gastroenterol 1990; 25: 245-250.
15. Dickey W, Stewart F, Nelson J, McBreen G, McMillan SA, Porter KG. Screening for coeliac disease as a possible maternal risk factor for neural tube defect. Clin Genet 1996; 49: 107-108.
16. Fanciulli G, Tomasi PA, Caucci F, Lai E, Sanciu F, Delitala G. Screening for celiac disease in patients with autoimmune thyroid disease: from research studies to daily clinical practice. Ann Ital Med Int 2005; 20: 39-44.
17. Fernandez-Banares F, Esteve-Comas M, Rosinach M. Screening for celiac disease in high risk groups. Gastroenterol Hepatol 2005; 28: 561-566.
18. Goldberg D, Kryszak D, Fasano A, Green PH. Screening for celiac disease in family members: is follow-up testing necessary? Dig Dis Sci 2007; 52: 1082-1086.
19. Mahmud FH, Murray JA, Kudva YC, et al. Celiac disease in type 1 diabetes mellitus in a North American community: prevalence, serologic screening, and clinical features. Mayo Clin Proc 2005; 80: 1429-1434.
20. Kawatu D, LeLeiko NS. Screening for celiac disease in asymptomatic children with Down syndrome: cost-effectiveness of preventing lymphoma. Pediatrics 2006; 118: 816-817.
21. Berti I, Della Vedova R, Paduano R, et al. Coeliac disease in primary care: evaluation of a case-finding strategy. Dig Liver Dis 2006; 38: 461-467.
22. Lanzini A, Villanacci V, Apillan N, et al. Epidemiological, clinical and histopathologic characteristics of celiac disease: results of a case-finding population-based program in an Italian community. Scand J Gastroenterol 2005; 40: 950-957.
23. Catassi C, Kryszak D, Louis-Jacques O, et al. Detection of Celiac disease in primary care: a multicenter case-finding study in North America. Am J Gastroenterol 2007; 102: 1454-1460.
24. McGough N, Cummings JH. Coeliac disease: a diverse clinical syndrome caused by intolerance of wheat, barley and rye. Proc Nutr Soc 2005; 64: 434-450.
25. Green PH. Where are all those patients with Celiac disease? Am J Gastroenterol 2007; 102: 1461-1463.
26. Vilppula A, Collin P, Maki M, et al. Undetected coeliac disease in the elderly: a biopsy-proven population-based study. Dig Liver Dis 2008; 40: 809-813.
27. Rostami K, Kerckhaert JP6, Tiemessen R, Meijer JW, Mulder CJ. The relationship between anti-endomysium antibodies and villous atrophy in coeliac disease using both monkey and human substrate. Eur J Gastroenterol Hepatol 1999; 11: 439-442.
28. Dickey W, Hughes DF, McMillan SA. Reliance on serum endomysial antibody testing underestimates the true prevalence of coeliac disease by one fifth. Scand J Gastroenterol 2000; 35: 181-183.
29. Tursi A, Brandimarte G, Giorgetti G, Gigliobianco A, Lombardi D, Gasbarrini G. Low prevalence of antigliadin and anti-endomysium antibodies in subclinical/silent celiac disease. Am J Gastroenterol 2001; 96: 1507-1510.
30. Abrams JA, Diamond B, Rotterdam H, Green PH. Seronegative celiac disease: increased prevalence with lesser degrees of villous atrophy. Dig Dis Sci 2004; 49: 546-550.
31. Rostami K, Steegers EA, Wong WY, Braat DD, Steegers-Theunissen RP. Coeliac disease and reproductive disorders: a neglected association. Eur J Obstet Gynecol Reprod Biol 2001; 96: 146-149.
32. Nelson M, Mendoza N, McGough N. A survey of provision of dietetic services for coeliac disease in the UK. J Hum Nutr Diet 2007; 20: 403-411.
33. Tiboni GM, de Vita MG, Faricelli R, Giampietro F, Liberati M. Serological testing for celiac disease in women undergoing assisted reproduction techniques. Hum Reprod 2006; 21: 376-379.
34. Bermejo Velasco PE, Burgos Garcia A. Neurological complications of celiac disease. Med Clin (Barc) 2006; 127: 500-507.
35. Briani C, Zara G, Toffanin E, et al. Neurological complications of celiac disease and autoimmune mechanisms: preliminary data of a prospective study in adult patients. Ann N Y Acad Sci 2005; 1051: 148-155.
36. Kumar V, Rajadhyaksha M, Wortsman J. Celiac disease-associated autoimmune endocrinopathies. Clin Diagn Lab Immunol 2001; 8: 678-685.
37. Li Voon Chong JS, Leong KS, Wallymahmed M, Sturgess R, MacFarlane IA. Is coeliac disease more prevalent in young adults with coexisting Type 1 diabetes mellitus and autoimmune thyroid disease compared with those with Type 1 diabetes mellitus alone? Diabet Med 2002; 19: 334-337.
38. Meize-Grochowski R. Celiac disease: a multisystem autoimmune disorder. Gastroenterol Nurs 2005; 28: 394-402.
39. Slate J, Hookman P, Barkin JS, Phillips RS. Systemic autoimmune disorders associated with celiac disease. Dig Dis Sci 2005; 50: 1705-1707.
40. Troncone R, Greco L, Mayer M, et al. Latent and potential coeliac disease. Acta Paediatr Suppl 1996; 412: 10-14.
41. Murray JA, Rubio-Tapia A, Van Dyke CT, et al. Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. Clin Gastroenterol Hepatol 2008; 6: 186-193.
42. Ciclitira PJ. Does clinical presentation correlate with degree of villous atrophy in patients with celiac disease? Nat Clin Pract Gastroenterol Hepatol 2007; 4: 482-483.

43. Sullivan PB, Marsh MN. Small intestinal mucosal histology in the syndrome of persistent diarrhoea and malnutrition: a review. Acta Paediatr Suppl 1992; 381: 72-77.
44. Carroccio A, Campisi G, Iacono G, et al. Oral mucosa of coeliac disease patients produces antiendomysial and antitransglutaminase antibodies: the diagnostic usefulness of an in vitro culture system. Aliment Pharmacol Ther 2007; 25: 1471-1477.
45. Savilahti E, Reunala T, Maki M. Increase of lymphocytes bearing the gamma/delta T cell receptor in the jejunum of patients with dermatitis herpetiformis. Gut 1992; 33: 206-211.
46. Verbeek WH, von Blomberg BM, Scholten PE, Kuik DJ, Mulder CJ, Schreurs MW. The presence of small intestinal intraepithelial gamma/delta T-lymphocytes is inversely correlated with lymphoma development in refractory celiac disease. Am J Gastroenterol. 2008; 103: 3152-3158.
47. Sbarbati A, Valletta E, Bertini M, et al. Gluten sensitivity and 'normal' histology: is the intestinal mucosa really normal? Dig Liver Dis 2003; 35: 768-773.
48. Freeman HJ. Pearls and pitfalls in the diagnosis of adult celiac disease. Can J Gastroenterol 2008; 22: 273-280.
49. Arentz-Hansen H, McAdam SN, Molberg O, et al. Celiac lesion T cells recognize epitopes that cluster in regions of gliadins rich in proline residues. Gastroenterology 2002; 123: 803-809.
50. Rostami K. From microenteropathy to villous atrophy: what is treatable? Dig Liver Dis 2003; 35: 758-759.
51. Santaolalla R, Fernandez-Banares F, Rodriguez R, et al. Diagnostic value of duodenal antitissue transglutaminase antibodies in gluten-sensitive enteropathy. Aliment Pharmacol Ther 2008; 27: 820-829.
52. Paparo F, Petrone E, Tosco A, et al. Clinical, HLA, and small bowel immunohistochemical features of children with positive serum antiendomysium antibodies and architecturally normal small intestinal mucosa. Am J Gastroenterol 2005; 100: 2294-2298.
53. Rostami K, Villanacci V. Microscopic enteritis: novel prospect in coeliac disease clinical and immuno-histogenesis. Evolution in diagnostic and treatment strategies. Dig Liver Dis 2009; 41: 245-252.
54. Spiegel BM, DeRosa VP, Gralnek IM, Wang V, Dulai GS. Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: a cost-effectiveness analysis. Gastroenterology 2004; 126: 1721-1732.
55. Mein SM, Ladabaum U. Serological testing for coeliac disease in patients with symptoms of irritable bowel syndrome: a cost-effectiveness analysis. Aliment Pharmacol Ther 2004; 19: 1199-1210.
56. Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. Eur J Gastroenterol Hepatol 2003; 15: 407-413.
57. Rostami K, Kerckhaert J, von Blomberg BM, Meijer JW, Wahab P, Mulder CJ. SAT and serology in adult coeliacs, seronegative coeliac disease seems a reality. Neth J Med 1998; 53: 15-19.
58. Hadithi M, von Blomberg BM, Crusius JB, et al. Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. Ann Intern Med 2007; 147: 294-302.
59. Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. Lancet 2001; 358: 1504-1508.